FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (MODIFIED)	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	X-11811
	U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5) 10/009720

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/15021	08 June 2000 (08.06.00)	15 July 1999 (15.07.99)

TITLE OF INVENTION: **PSEUDOMYCIN AMIDE AND ESTER ANALOGS**

APPLICANT(S) FOR DO/EO/US: **Shu Hui Chen, Christopher Stanley Galka, Sarah Lynne Hellman, John L. Krstenansky, Michael John Rodriguez, Xicheng David Sun, Alexander Ya Usyatinsky, Venkatraghavan Vasudevan, and Mark James Zweifel**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [X] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [X] A copy of the International Preliminary Examination Report (IPER), including any annexes, and, if not in English, an English language translation of the annexes to the IPER under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information:

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/009720	PCT/US00/15021	X-11811

17. [X] The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. **$1040.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **$740.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**

International preliminary examination fee paid to USPTO (37 CRF 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$100.00**

ENTER APPROPRIATE BASIC FEE AMOUNT = $ **890.00**

Surcharge of **$130.00** for furnishing the oath or declaration later than __20 __30 months from the earliest claimed priority date (37 CFR 1.492(e)). $

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	13 -20=	0	X $18.00	$
Independent claims	6 - 3=	3	X $84.00	$ 252.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $280.00	$

TOTAL OF ABOVE CALCULATIONS = $ **252.00**

Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28). $

SUBTOTAL = $ **1,142.00**

Processing fee of **$130.00** for furnishing English translation later than __ 20 __30 months from the earliest claimed priority date (37 CFR 1.492(f)). + $

TOTAL NATIONAL FEE = $ **1,142.00**

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property $

TOTAL FEES ENCLOSED = $ **1,142.00**

Amount to be refunded $

charged $

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 05-0840 in the amount of **$ 1,142.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 05-0840. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
ELI LILLY AND COMPANY
PATENT DIVISION/1104
LILLY CORPORATE CENTER
INDIANAPOLIS, INDIANA 46285

13 Dec 2001
Date

25885
PATENT TRADEMARK OFFICE

SIGNATURE

Tina M. Tucker
NAME

47,145
REGISTRATION NUMBER

(317) 277-3537
TELEPHONE NUMBER

"Express Mail" mailing label number EL 230530020 US

Date of Deposit Dec. 13, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Printed Name Signature

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Chen, et al.	
Serial No.:	Unknown	
Filed:	June 8, 2000	Group Art Unit: Unknown
For:	Pseudomycin Amide And Ester Analogs	Examiner: Unknown
Docket No.:	X-11811	

Preliminary Amendment

Assistant Commissioner for Patents
Washington, D. C. 20231

Sir:

Applicants submit the following preliminary amendments and remarks in connection with the filing of the above-identified application.

Please amend the application as follows:

In the Specification

On page 4 of the specification, after the sentence, "R^c is hydrogen, hydroxy, C_1-C_4 alkoxy…;" please insert the following

--R^d is hydrogen;--

On page 7 of the specification, line 24, please replace "an antifungal" with "a fungal".

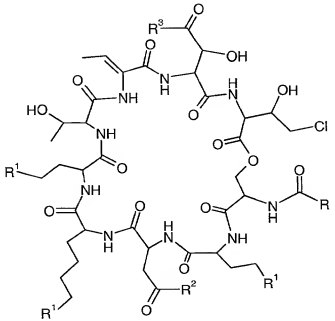
On page 22 of the specification, line 19, please insert "PCT/US00/15017" for the blank serial number.

In the Claims

Please cancel Claim 7 without prejudice or disclaimer of any of the subject matter contained herein.

Please amend the claims as follows:

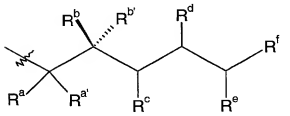
1. (Amended) A pseudomycin compound having the following structure I



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl

ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

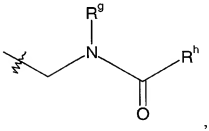
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_8-C_{18} alkyl, or C_5-C_{11} alkoxy;

R is



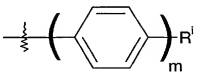
,

where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

R is

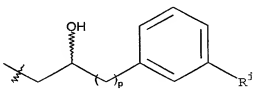


,

where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

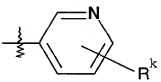


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –$C(O)CH_3$;

R^1 is independently -NH_2 or -NH_p-Pg, where p is 0 or 1;

R^2 and R^3 are independently -OR^{2a}, or -$N(R^{2b})(R^{2c})$,

where

R^{2a} and R^{2b} are independently hydrogen, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, hydroxy(C_1-C_{10})alkyl, alkoxy(C_1-C_{10})alkyl, C_2-C_{10} alkenyl, amino(C_1-C_{10})alkyl, mono- or di-alkylamino(C_1-C_{10})alkyl, aryl(C_1-C_{10})alkyl, heteroaryl(C_1-C_{10})alkyl, or cycloheteroalkyl(C_1-C_{10})alkyl, or

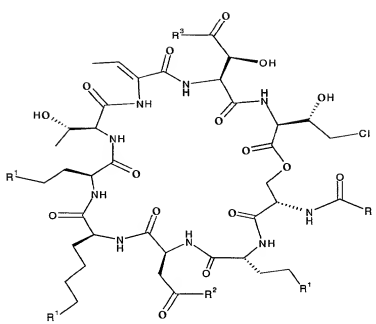
R^{2b} is an alkyl carboxylate residue of an aminoacid alkyl ester, and

R^{2c} is hydrogen or C_1-C_6 alkyl,

provided that both R^2 and R^3 are not -OH; and

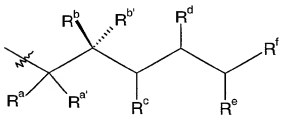
pharmaceutically acceptable salts and solvates thereof.

2. (Amended) A pseudomycin prodrug having the following structure



wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

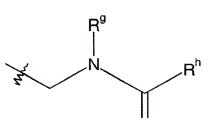
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_8-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

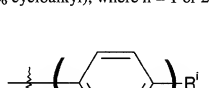


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

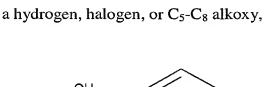
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

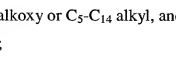


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

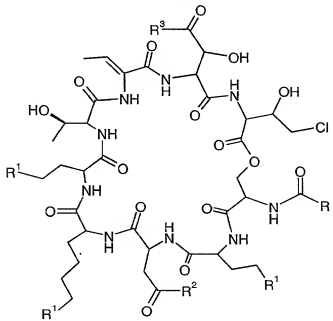
R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –$C(O)CH_3$;

R^1 is independently -NH_2 or -NH_p-Pg, where p is 0 or 1;

R^2 and R^3 are $-OR^{2a}$, where R^{2a} is C_1-C_3 alkyl; and pharmaceutically acceptable salts and solvates thereof.

3. (Amended) A 3-amido derivative of a pseudomycin compound prepared by the steps of

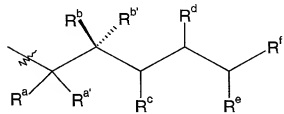
(i) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

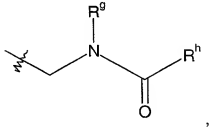
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

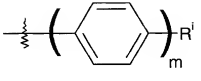


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

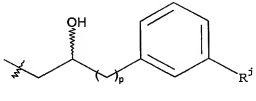
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

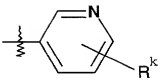


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –

C(C)CH_3;

R^1 is -NH_2;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

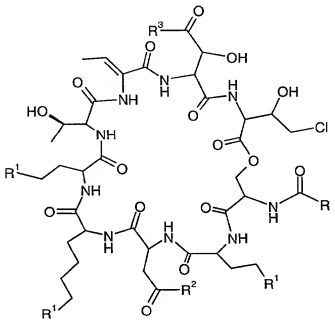
(ii) protecting the amino groups, R^1, at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 3 using *o*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate or 2(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate as a coupling agent;

(iv) removing said amino-protecting groups.

6. (Amended) An 8-amido derivative of a pseudomycin compound prepared by the steps of

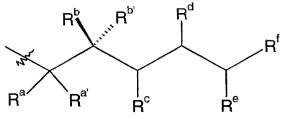
(i) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

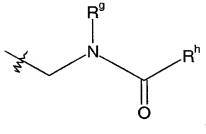
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

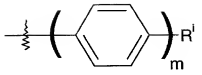


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

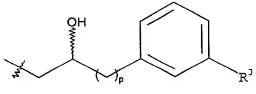
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

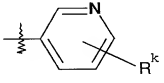


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is $-(CH_2)-NR^m-(C_{13}$-C_{18} alkyl), where R^m is H, $-CH_3$ or $-C(C)CH_3$;

R^1 is $-NH_2$;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

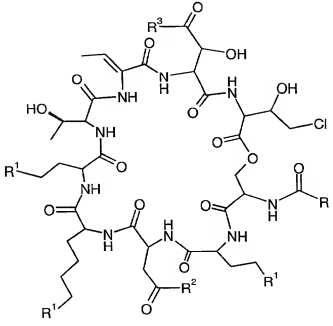
(ii) protecting the amino groups at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 8 using benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate as a coupling agent;

(iv) removing said amino-protecting groups.

8. (Amended) A process for making a 3-amido derivative of a pseudomycin compound comprising the steps of

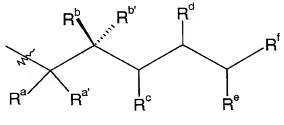
(i) providing a pseudomycin compound having the following structure



I

wherein

R is



,

where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

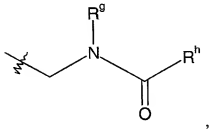
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is



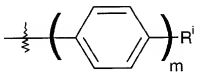
,

where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

R is

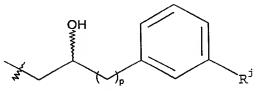


,

where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

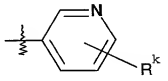


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –

C(C)CH_3;

R^1 is -NH_2;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

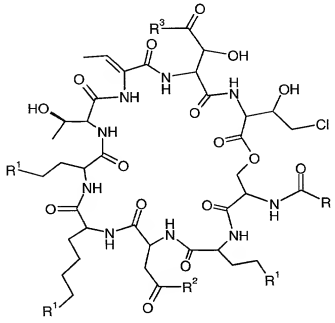
(ii) protecting the amino groups, R^1, at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 3 using *o*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate or 2(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate as a coupling agent in the presence of a bulky amine and at a temperature between about 0°C and -20°C;

(iv) removing said amino-protecting groups.

9. (Amended) A process for making an 8-amido derivative of a pseudomycin compound comprising the steps of

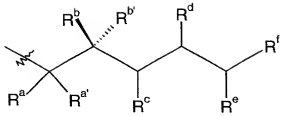
(ii) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

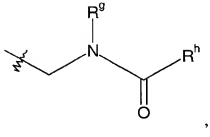
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

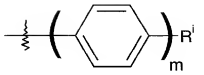


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

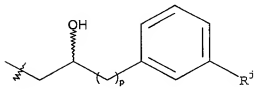
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

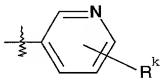


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –C(C)CH_3;

R^1 is -NH_2;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

(ii) protecting the amino groups at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 8 using benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate as a coupling agent;

(iv) removing said amino-protecting groups.

10. (Amended) A pharmaceutical formulation comprising said compound of Claim 1 or said pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier, buffer, diluent or excipient.

11. (Amended) A pharmaceutical formulation comprising said prodrug of Claim 2 or said pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier, buffer, diluent or excipient.

12. (Amended) A method for treating a fungal infection in an animal in need thereof, which comprises administering to said animal said pseudomycin compound or said pharmaceutically acceptable salt or solvate thereof of Claim 1.

13. (Amended) A method for treating a fungal infection in an animal in need thereof, which comprises administering to said animal said prodrug or said pharmaceutically acceptable salt or solvate thereof of Claim 2.

REMARKS

Claim 7 has been canceled. Claims 1-3, 6, and 8-13 have been amended. Thus, claims 1-6 and 8-13 are presently in the application.

In regard to claims 1-3, 6, and 8-9, the variable "R^d" was included in the definition of "R", but the definition of R^d, itself, was inadvertently omitted. However, support for amending the aforementioned claims to include a definition of R^d can be found in the definition of "R^c" in claim 1 as originally filed. Inasmuch as R^c and R^c may form a six-membered aromatic ring, R^d, thus, must at least be hydrogen. As such, claims 1-3, 6, and 8-9 and the specification at page 4 have been amended to recite hydrogen.

In regard to claims 10 and 11, these claims have been amended to include a pharmaceutically acceptable salt or solvate thereof, a buffer, a diluent or a excipient in the formulation. Basis for the amendment can be found in claim 1 and on page 27, lines 10-21. Additionally, claims 10 and 11 were amended to correct antecedent basis ("a" has been replaced by "said").

In regard to claims 12-13, these claims were amended to correct obvious typographical errors ("an antifungal" infection has been replaced by "a fungal" infection and in claim 12 "aminal" has been replaced by "animal"). Likewise, the specification on page 7, line 24, was amended to correct one of the same errors ("an antifungal" infection has been replaced by "a fungal" infection). Basis for these amendments can be found on page 28, lines 23-24 and page 29, lines 1-18. Additionally, claims 12-13 were amended to correct

antecedent basis ("a" has been replaced by "said") and to make it clear that pharmaceutically acceptable salts and solvates are included in the claim.

Additionally, the specification has been amended at page 22 to indicate a PCT application number, unavailable at the time of filing the present application.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

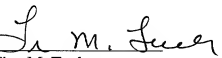
For the Examiner's convenience, a clean claim set is attached.

Early and favorable action on the merits is respectfully requested.

Please charge any fees or credit any overpayment in connection with this application which may be required by this or any related paper to Deposit Account No. 05-0840.

If the Examiner has any questions, or would like to discuss any matters in connection with this application, he or she is invited to contact the undersigned at (317) 277-3537.

Respectfully submitted,



Tina M. Tucker
Agent for Applicants
Registration No. 47,145
Phone: 317-277-3537

Eli Lilly and Company
Patent Division/TMT
Lilly Corporate Center
Indianapolis, Indiana 46285

16 Nov 2001

Attachments: Clean Claim Set

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

On page 4 of the specification, after the sentence, "R^c is hydrogen, hydroxy, C_1-C_4 alkoxy…;" please insert the following

--R^d is hydrogen;--

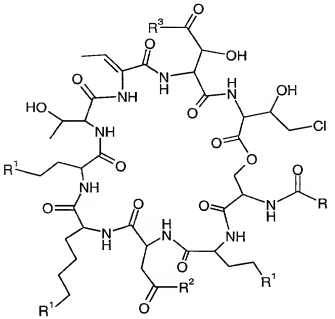
On page 7 of the specification, line 24, please replace "an antifungal" with "a fungal".

On page 22 of the specification, line 19, please insert "PCT/US00/15017" for the blank serial number.

In the claims:

Claim 7 has been cancelled.

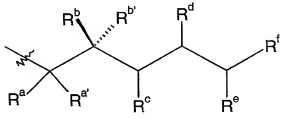
1. (Amended) A pseudomycin compound having the following structure I



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

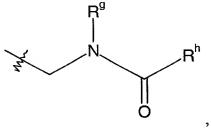
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_8-C_{18} alkyl, or C_5-C_{11} alkoxy;

R is

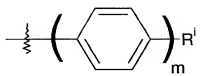


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

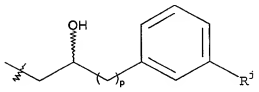
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

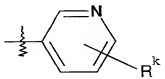


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –$C(O)CH_3$;

R^1 is independently -NH_2 or -NH_p-Pg, where p is 0 or 1;

R^2 and R^3 are independently -OR^{2a}, or -$N(R^{2b})(R^{2c})$,

where

R^{2a} and R^{2b} are independently hydrogen, C_1-C_{10} alkyl, C_3.C_6 cycloalkyl, hydroxy(C_1-C_{10})alkyl, alkoxy(C_1-C_{10})alkyl, C_2-C_{10} alkenyl, amino(C_1-C_{10})alkyl, mono- or di-alkylamino(C_1-C_{10})alkyl, aryl(C_1-C_{10})alkyl, heteroaryl(C_1-C_{10})alkyl, or cycloheteroalkyl(C_1-C_{10})alkyl, or

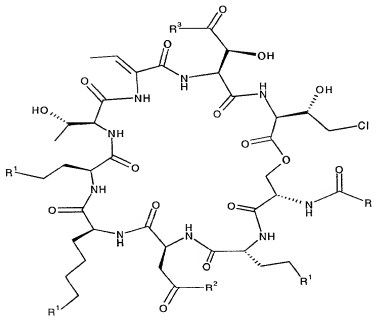
R^{2b} is an alkyl carboxylate residue of an aminoacid alkyl ester, and

R^{2c} is hydrogen or C_1-C_6 alkyl,

provided that both R^2 and R^3 are not -OH; and

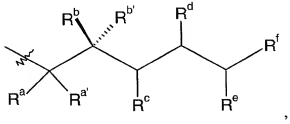
pharmaceutically acceptable salts and solvates thereof.

2. (Amended) A pseudomycin prodrug having the following structure



wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

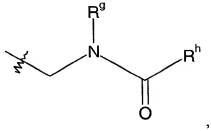
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_8-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

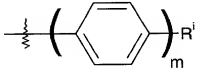


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

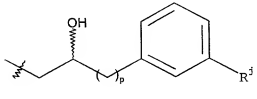
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

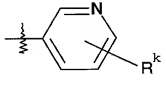


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –$C(O)CH_3$;

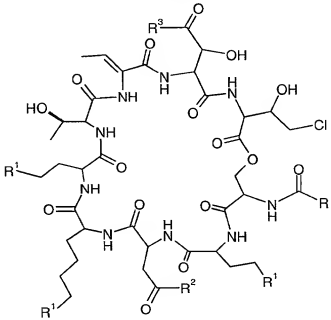
R^1 is independently $-NH_2$ or $-NH_p$-Pg, where p is 0 or 1;

R^2 and R^3 are $-OR^{2a}$, where R^{2a} is C_1-C_3 alkyl; and

pharmaceutically acceptable salts and solvates thereof.

3. (Amended) A 3-amido derivative of a pseudomycin compound prepared by the steps of

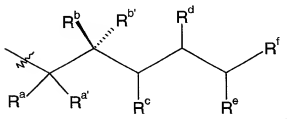
(i) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

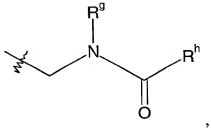
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is



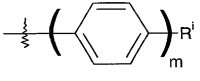
,

where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

R is

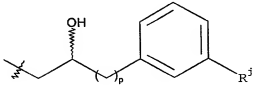


,

where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

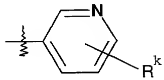


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –C(C)CH_3;

R^1 is -NH_2;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

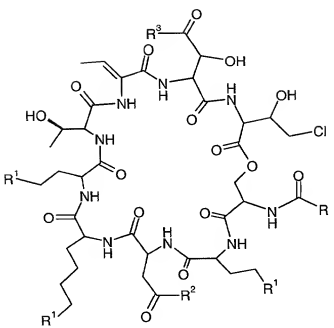
(ii) protecting the amino groups, R^1, at positions 2, 4 and 5 with an amino-protecting group;

(iii)forming an amide linkage at position 3 using *o*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate or 2(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate as a coupling agent;

(iv) removing said amino-protecting groups.

6. (Amended) An 8-amido derivative of a pseudomycin compound prepared by the steps of

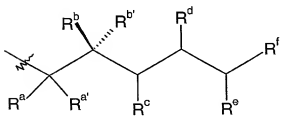
(iii) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

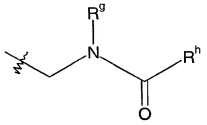
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

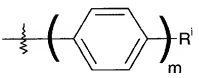


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

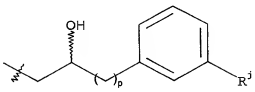
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

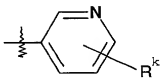


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is $-(CH_2)-NR^m-(C_{13}-C_{18}$ alkyl), where R^m is H, $-CH_3$ or $-C(C)CH_3$;

R^1 is $-NH_2$;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

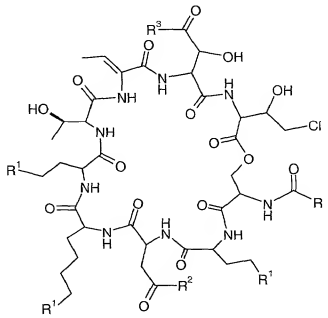
(ii) protecting the amino groups at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 8 using benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate as a coupling agent;

(iv) removing said amino-protecting groups.

8. (Amended) A process for making a 3-amido derivative of a pseudomycin compound comprising the steps of

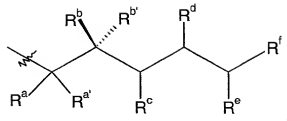
(i) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

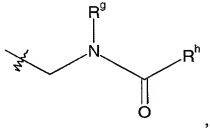
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

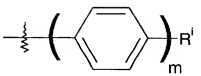


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

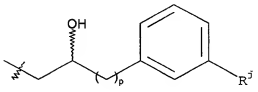
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

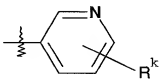


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –C(C)CH_3;

R^1 is -NH_2;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

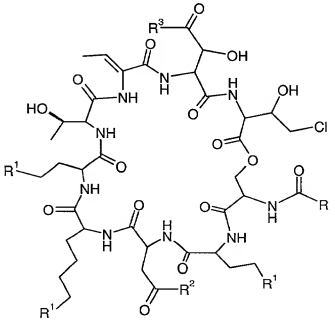
(ii) protecting the amino groups, R^1, at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 3 using *o*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate or 2(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate as a coupling agent in the presence of a bulky amine and at a temperature between about 0°C and -20°C;

(iv) removing said amino-protecting groups.

9. (Amended) A process for making an 8-amido derivative of a pseudomycin compound comprising the steps of

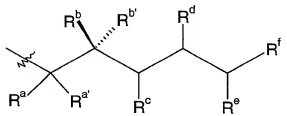
(iv) providing a pseudomycin compound having the following structure



I

wherein

R is



,

where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

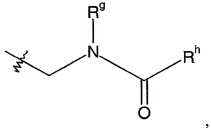
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is



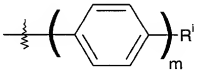
,

where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

R is

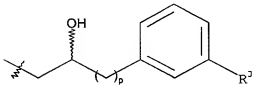


,

where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

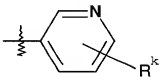


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –

C(C)CH_3;

R^1 is -NH_2;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

(ii) protecting the amino groups at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 8 using benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate as a coupling agent;

(iv) removing said amino-protecting groups.

10. (Amended) A pharmaceutical formulation comprising [a] said compound of Claim 1 [and a] or said pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier, buffer, diluent or excipient.

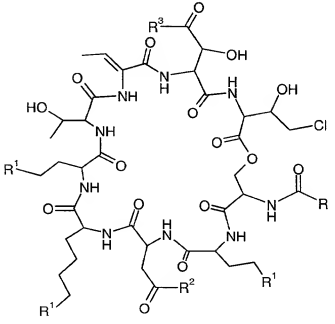
11. (Amended) A pharmaceutical formulation comprising [a] said prodrug of Claim 2 [and a] or said pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier, buffer, diluent or excipient.

12. (Amended) A method for treating [an antifungal] a fungal infection in an [aminal] animal in need thereof, which comprises administering to said animal [a] said pseudomycin compound or said pharmaceutically acceptable salt of solvate thereof of Claim 1.

13. (Amended) A method for treating [an antifungal] a fungal infection in an animal in need thereof, which comprises administering to said animal [a] said prodrug or said pharmaceutically acceptable salt of solvate thereof of Claim 2.

CLEAN CLAIM SET

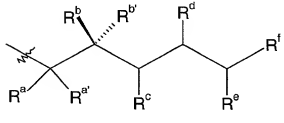
1. A pseudomycin compound having the following structure I



I

wherein

R is



,

where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

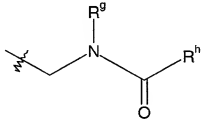
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_8-C_{18} alkyl, or C_5-C_{11} alkoxy;

R is

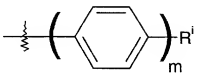


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

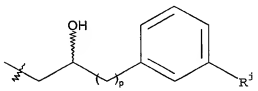
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

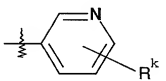


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –C(O)CH_3;

R^1 is independently -NH_2 or -NH_p-Pg, where p is 0 or 1;

R^2 and R^3 are independently -OR^{2a}, or -$N(R^{2b})(R^{2c})$,

where

R^{2a} and R^{2b} are independently hydrogen, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, hydroxy(C_1-C_{10})alkyl, alkoxy(C_1-C_{10})alkyl, C_2-C_{10} alkenyl, amino(C_1-C_{10})alkyl, mono- or di-alkylamino(C_1-C_{10})alkyl, aryl(C_1-C_{10})alkyl, heteroaryl(C_1-C_{10})alkyl, or cycloheteroalkyl(C_1-C_{10})alkyl, or

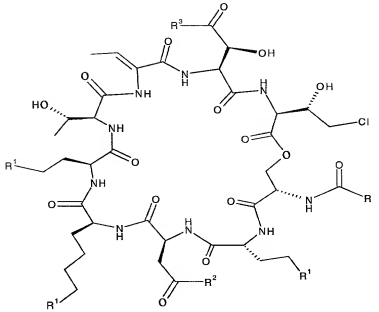
R^{2b} is an alkyl carboxylate residue of an aminoacid alkyl ester, and

R^{2c} is hydrogen or C_1-C_6 alkyl,

provided that both R^2 and R^3 are not -OH; and

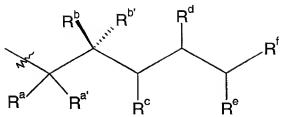
pharmaceutically acceptable salts and solvates thereof.

2. A pseudomycin prodrug having the following structure



wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

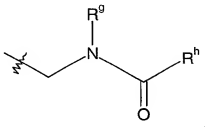
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_8-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

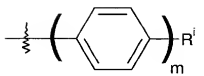


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

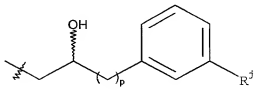
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

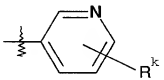


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –C(O)CH_3;

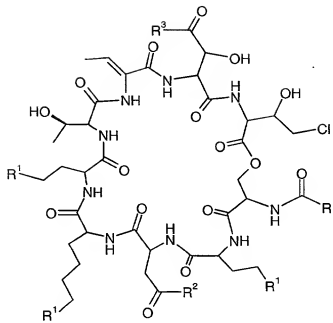
R^1 is independently -NH_2 or -NH_p-Pg, where p is 0 or 1;

R^2 and R^3 are -OR^{2a}, where R^{2a} is C_1-C_3 alkyl; and

pharmaceutically acceptable salts and solvates thereof.

3. A 3-amido derivative of a pseudomycin compound prepared by the steps of

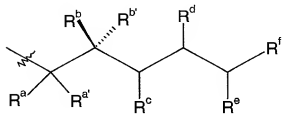
(i) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

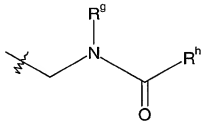
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

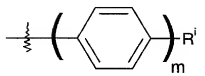


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

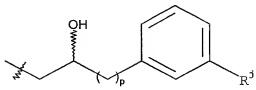
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

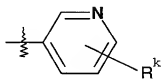


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –C(C)CH_3;

R^1 is -NH_2;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

(ii) protecting the amino groups, R^1, at positions 2, 4 and 5 with an amino-protecting group;

(iii)forming an amide linkage at position 3 using *o*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate or 2(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate as a coupling agent;

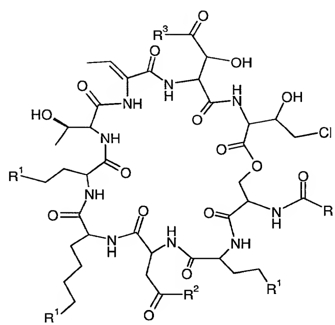
(iv) removing said amino-protecting groups.

4. The 3-amido derivative of Claim 3 wherein step (iii) forming an amide linkage is accomplished in the presence of a bulky amine.

5. The 3-amido derivative of Claim 3 wherein step (iii) forming an amide linkage is accomplished in the presence of a bulky amine and at a temperature between about 0°C and -20°C.

6. An 8-amido derivative of a pseudomycin compound prepared by the steps of

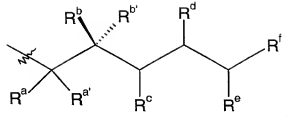
(v) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

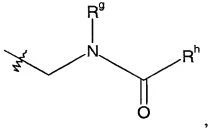
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is



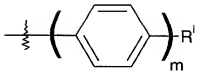
where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2;

or

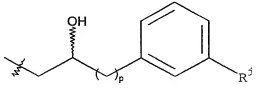
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

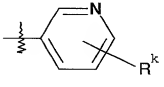


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –C(C)CH_3;

R^1 is -NH_2;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

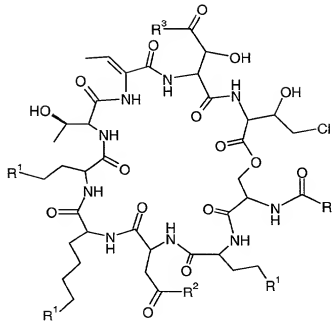
(ii) protecting the amino groups at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 8 using benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate as a coupling agent;

(iv) removing said amino-protecting groups.

8. A process for making a 3-amido derivative of a pseudomycin compound comprising the steps of

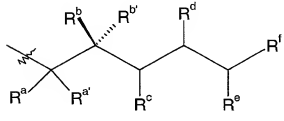
(i) providing a pseudomycin compound having the following structure



I

wherein

R is



,

where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

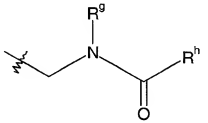
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

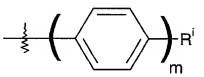


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

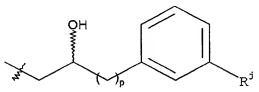
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

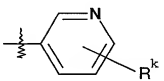


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is -(CH_2)-NR^m-(C_{13}-C_{18} alkyl), where R^m is H, -CH_3 or –C(C)CH_3;

R^1 is -NH_2;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

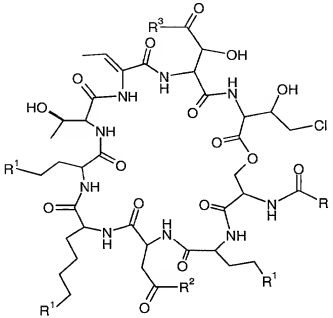
(ii) protecting the amino groups, R^1, at positions 2, 4 and 5 with an amino-protecting group;

(iii)forming an amide linkage at position 3 using *o*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate or 2(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate as a coupling agent in the presence of a bulky amine and at a temperature between about 0°C and -20°C;

(iv) removing said amino-protecting groups.

9. A process for making an 8-amido derivative of a pseudomycin compound comprising the steps of

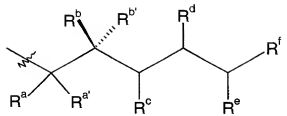
(vi) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

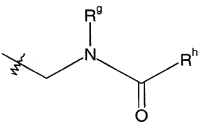
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^d is hydrogen;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

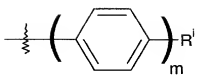


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

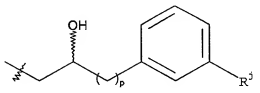
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

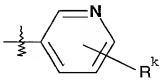


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is $-(CH_2)-NR^m-(C_{13}$-C_{18} alkyl), where R^m is H, $-CH_3$ or $-C(C)CH_3$;

R^1 is $-NH_2$;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

(ii) protecting the amino groups at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 8 using benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate as a coupling agent;

(iv) removing said amino-protecting groups.

10. A pharmaceutical formulation comprising said compound of Claim 1 or said pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier, buffer, diluent or excipient.

11. A pharmaceutical formulation comprising said prodrug of Claim 2 or said pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier, buffer, diluent or excipient.

12. A method for treating a fungal infection in an animal in need thereof, which comprises administering to said animal said pseudomycin compound or said pharmaceutically acceptable salt of solvate thereof of Claim 1.

13. A method for treating a fungal infection in an animal in need thereof, which comprises administering to said animal said prodrug or said pharmaceutically acceptable salt of solvate thereof of Claim 2.

PSEUDOMYCIN AMIDE & ESTER ANALOGS

FIELD OF THE INVENTION

The present invention relates to pseudomycin compounds, in particular, acid-modified, semi-synthetic pseudomycin compounds.

BACKGROUND OF THE INVENTION

Pseudomycins are natural products isolated from liquid cultures of *Pseudomonas syringae* (plant-associated bacterium) and have been shown to have antifungal activities. (see i.e., Harrison, L., et al., "Pseudomycins, a family of novel peptides from *Pseudomonas syringae* possessing broad-spectrum antifungal activity," J. Gen. Microbiology, **137**(12), 2857-65 (1991) and US Patent Nos. 5,576,298 and 5,837,685) Unlike the previously described antimycotics from *P. syringae* (e.g., syringomycins, syringotoxins and syringostatins), pseudomycins A-C contain hydroxyaspartic acid, aspartic acid, serine, dehydroaminobutyric acid, lysine and diaminobutyric acid.

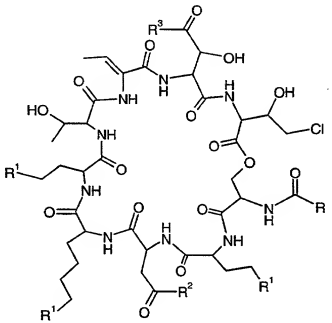
The peptide moiety for pseudomycins A, A', B, B', C, C' corresponds to L-Ser-D-Dab-L-Asp-L-Lys-L-Dab-L-aThr-Z-Dhb-L-Asp(3-OH)-L-Thr(4-Cl) with the terminal carboxyl group closing a macrocyclic ring on the OH group of the N-terminal

Ser. The analogs are distinguished by the N-acyl side chain, i.e., pseudomycin A is N-acylated by 3,4-dihydroxytetradeconoyl, pseudomycin A' by 3,4-dihydroxypentadecanoyl, pseudomycin B by 3-hydroxytetradecanoyl, pseudomycin B' by 3-hydroxydodecanoyl, pseudomycin C by 3,4-dihydroxyhexadecanoyl and pseudomycin C' by 3-hydroxyhexadecanoyl. (see i.e., Ballio, A., et al., "Novel bioactive lipodepsipeptides from *Pseudomonas syringae*: the pseudomycins," FEBS Letters, **355**(1), 96-100, (1994) and Coiro, V.M., et al., "Solution conformation of the *Pseudomonas syringae* MSU 16H phytotoxic lipodepsipeptide Pseudomycin A determined by computer simulations using distance geometry and molecular dynamics from NMR data," Eur. J. Biochem., **257**(2), 449-456 (1998).)

Pseudomycins are known to have certain adverse biological effects. For example, destruction of the endothelium of the vein, destruction of tissue, inflammation, and local toxicity to host tissues have been observed when pseudomycin is administered intraveneously. Since the pseudomycins have proven antifungal activity and relatively unexplored chemistry, there is a need to explore this class of compounds for other potential compounds that may be useful as antifungal agents having less adverse side affects.

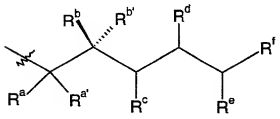
BRIEF SUMMARY OF THE INVENTION

The present invention provides pseudomycin compounds represented by the following structure which are useful as antifungal agents or in the design of antifungal agents.



I

wherein R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-

membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

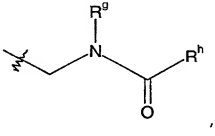
R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy, or biphenyl;

R is



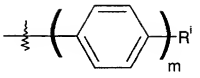
,

where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

R is

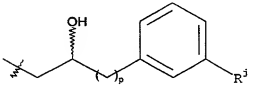


where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and

m is 1, 2 or 3;

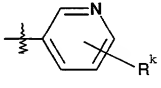
R is



where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is $-(CH_2)-NR^m-(C_{13}-C_{18}$ alkyl), where R^m is H, $-CH_3$ or $-C(O)CH_3$;

R^1 is independently $-NH_2$ or $-NH_p$-Pg, where p is 0 or 1;

R^2 and R^3 are independently $-OR^{2a}$, or $-N(R^{2b})(R^{2c})$,

where

R^{2a} and R^{2b} are independently hydrogen, C_1-C_{10} alkyl (e.g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, *n*-amyl, *i*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonanyl, *n*-decyl, etc.), C_3-C_6 cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclopentylmethyl, methylcyclopentyl, cyclohexyl, etc.) haloalkyl (e.g., CF_3CH_2-), hydroxy(C_1-C_{10})alkyl, alkoxy(C_1-C_{10})alkyl (e.g, methoxyethyl), allyl, C_2-C_{10} alkenyl, amino(C_1-C_{10})alkyl, mono- or di-alkylamino(C_1-C_{10})alkyl, aryl(C_1-C_{10})alkyl (e.g., benzyl), heteroaryl(C_1-C_{10})alkyl (e.g., 3-pyridylmethyl, 4-pyridylmethyl), or cycloheteroalkyl(C_1-C_{10})alkyl (e.g., N-tetrahydro-1,4-oxazinylethyl and N-piperazinylethyl), or

R^{2b} is an alkyl carboxylate residue of an aminoacid alkyl ester (e.g., $-CH_2CO_2CH_3$, $-CH(CO_2CH_3)CH(CH_3)_2$, $-CH(CO_2CH_3)CH(phenyl)$, $-CH(CO_2CH_3)CH_2OH$, $-CH(CO_2CH_3)CH_2$(*p*-hydroxyphenyl), $-CH(CO_2CH_3)CH_2SH$, $-CH(CO_2CH_3)CH_2(CH_2)_3NH_2$, $-CH(CO_2CH_3)CH_2$(4- or 5-imidazole), $-CH(CO_2CH_3)CH_2CO_2CH_3$, $-CH(CO_2CH_3)CH_2CO_2NH_2$, and the like), and

R^{2c} is hydrogen or C_1-C_6 alkyl,

provided that both R^2 and R^3 are not -OH; and

pharmaceutically acceptable salts and solvates thereof.

In another embodiment of the present invention, a prodrug of a pseudomycin compound is provided having structure I represented above wherein R^2 and R^3 are represented by $-OR^{2a}$, where R^{2a} is C_1-C_3 alkyl.

In yet another embodiment of the present invention, a 3-amido derivative of a pseudomycin compound is provided where the compound is prepared by the steps of (i) providing a compound having structure I above wherein R^1 is $-NH_2$ and R^2 and R^3 are both -OH; (ii) protecting the amino groups, R^1, at positions 2, 4 and 5 with an amino-protecting group; (iii) forming an amide linkage at position 3 using an *o*-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate as a coupling agent; and (iv) removing the amino-protecting groups. An 8-amido derivative is also provided where the derivative is prepared using the steps described above except using benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate as the coupling agent.

In another embodiment of the present invention, a pharmaceutical formulation is provided which includes the pseudomycin compound represented by structure I above and a pharmaceutically acceptable carrier.

In yet another embodiment of the present invention, a method is provided for treating an antifungal infection in

an animal in need thereof, which comprises administering to the animal the pseudomycin compound I described above.

Definitions

As used herein, the term "alkyl" refers to a hydrocarbon radical of the general formula C_nH_{2n+1} containing from 1 to 30 carbon atoms unless otherwise indicated. The alkane radical may be straight (e.g. methyl, ethyl, propyl, butyl, etc.), branched (e.g., isopropyl, isobutyl, tertiary butyl, neopentyl, etc.), cyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, methylcyclopentyl, cyclohexyl, etc.), or multi-cyclic (e.g., bicyclo[2.2.1]heptane, spiro[2.2]pentane, etc.). The alkane radical may be substituted or unsubstituted. Similarly, the alkyl portion of an alkoxy group, alkanoyl, or alkanoate have the same definition as above.

The term "alkenyl" refers to an acyclic hydrocarbon containing at least one carbon carbon double bond. The alkene radical may be straight, branched, cyclic, or multi-cyclic. The alkene radical may be substituted or unsubstituted. The alkenyl portion of an alkenoxy, alkenoyl or alkenoate group has the same definition as above.

The term "alkynyl" refers to an acyclic hydrocarbon containing at least one carbon carbon triple bond. The alkyne radical may be straight, or branched. The alkyne radical may be substituted or unsubstituted. The alkynyl

portion of an alkynoxy, alkynoyl or alkynoate group has the same definition as above.

The term "aryl" refers to aromatic moieties having single (e.g., phenyl) or fused ring systems (e.g., naphthalene, anthracene, phenanthrene, etc.). The aryl groups may be substituted or unsubstituted.

The term "heteroaryl" refers to aromatic moieties containing at least one heteratom within the aromatic ring system (e.g., pyrrole, pyridine, indole, thiophene, furan, benzofuran, imidazole, oxazine, pyrimidine, purine, benzimidazole, quinoline, etc.). The aromatic moiety may consist of a single or fused ring system. The heteroaryl groups may be substituted or unsubstituted.

"NH_p-Pg" and "amino protecting group" refer to a substituent of the amino group (Pg) commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. When p is 0, the amino protecting group, when taken with the nitrogen to which it is attached, forms a cyclic imide, *e.g.*, phthalimido and tetrachlorophthalimido. When p is 1, the protecting group, when taken with the nitrogen to which it is attached, can form a carbamate, *e.g.*, methyl, ethyl, and 9-fluorenylmethylcarbamate; or an amide, *e.g.*, N-formyl and N-acetylamide.

Within the field of organic chemistry and particularly within the field of organic biochemistry, it is widely understood that significant substitution of compounds is tolerated or even useful. In the present invention, for example, the term alkyl group allows for substitutents which is a classic alkyl, such as methyl, ethyl, propyl, hexyl, isooctyl, dodecyl, stearyl, etc. The term "group" specifically envisions and allows for substitutions on alkyls which are common in the art, such as hydroxy, halogen, alkoxy, carbonyl, keto, ester, carbamato, etc., as well as including the unsubstituted alkyl moiety. However, it is generally understood by those skilled in the art that the substituents should be selected so as to not adversely affect the pharmacological characteristics of the compound or adversely interfere with the use of the medicament. Suitable substituents for any of the groups defined above include alkyl, alkenyl, alkynyl, aryl, halo, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, mono- and di-alkyl amino, quaternary ammonium salts, aminoalkoxy, hydroxyalkylamino, aminoalkylthio, carbamyl, carbonyl, carboxy, glycolyl, glycyl, hydrazino, guanyl, and combinations thereof.

The term "solvate" refers to an aggregate that comprises one or more molecules of the solute, such as a compound of structure I, with one or more molecules of a

pharmaceutical solvent, such as water, ethanol, and the like.

The term "pharmaceutically acceptable salt" refers to organic or inorganic salts of the compounds represented by structure I that are substantially non-toxic to the recipient at the doses administered.

The term "prodrug" refers to a class of drugs which result in pharmacological action due to conversion by metabolic processes within the body (i.e., biotransformation). In the present invention, the pseudomycin prodrug compounds contain ester functionalities that can be cleaved by esterases in the plasma to produce the active drug.

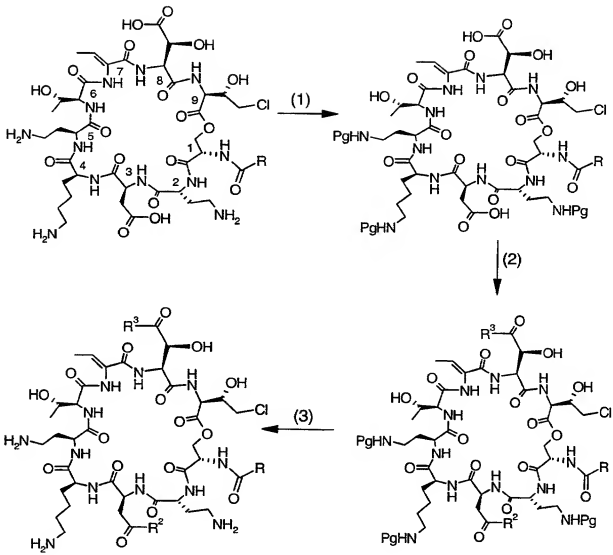
The term "animal" refers to humans, companion animals (e.g., dogs, cats and horses), food-source animals (e.g., cows, pigs, sheep and poultry), zoo animals, marine animals, birds and other similar animal species.

DETAILED DESCRIPTION OF THE INVENTION

Applicants have discovered that modification of the acid functionality attached to the hydroxyaspartic acid and/or aspartic acid units of a pseudomycin natural product or semi-synthetic derivative provides compounds having *in vitro* indications which suggest that the new compounds may be active against *C. albican, C, neoformans,* and/or *A.*

fumigatus. Some bis-esters have been shown to act as a prodrug; therefore, these particular compounds have reduced *in vitro* activity but show *in vivo* efficacy.

Scheme I below illustrates the general procedures for synthesizing Compound I from any one of the naturally occurring pseudomycins or N-acyl modified derivatives. In general, three synthetic steps are used to produce Compound I: (1) selective amino protection; (2) condensation with the appropriate alcohol or amine to produce the respective ester or amide; and (4) deprotection of the amino groups.



Scheme I

The pendant amino groups at residues 2, 4 and 5 may be protected using any standard means known to those skilled in the art for amino protection. The exact genus and species of amino protecting group employed is not critical so long as the derivatized amino group is stable to the conditions of subsequent reaction(s) on other positions of the intermediate molecule and the protecting group can be selectively removed at the appropriate point without

disrupting the remainder of the molecule including any other amino protecting group(s). Preferred amino protecting groups are *t*-butoxycarbonyl (*t*-Boc), allyloxycarbonyl, phthalimido, and benzyloxycarbonyl (CBZ). Most preferred is allyloxycarbonyl (Alloc) and benzyloxycarbonyl (CBZ). Further examples of suitable protecting groups are described in T.W. Greene, "Protective Groups in Organic Synthesis," John Wiley and Sons, New York, N.Y., (2nd ed., 1991), at chapter 7.

Formation of the ester groups may be accomplished using standard esterification procedures well-known to those skilled in the art. Esterification under acidic conditions typically includes dissolving or suspending the pseudomycin compound in the appropriate alcohol in the presence of a protic acid (e.g., HCl, TFA, p-toluenesulfonic acid, etc.). Under basic conditions, the pseudomycin compound is generally reacted with the appropriate alkyl halide in the presence of a weak base (e.g., sodium bicarbonate under anhydrous conditions).

Formation of the amide groups may be accomplished using standard amidation procedures well-known to those skilled in the art. However, the choice of coupling agents provides selective modification of the acid groups. For example, the use of benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate(PyBOP) as the coupling agent allows one

to isolate pure mono-amides at residue 8 and (in some cases) pure bis amides simultaneously. Whereas, coupling agents such as *o*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) and 2(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate (HBTU) favor formation of monoamides at residue 3.

Applicants also discovered that the addition of a bulky amine enhances the ratio of monoamides at residue 3. The ratio of amidation at residue 3 vs. residue 8 increased from about 1:1 to about 6:1 and the amount of bis-amides was reduced through the addition of a bulky amine. The term "bulky amine" refers to an amine having multiple and/or large substituents on the nitrogen atom. Any tertiary amine may be used that is compatible with the reaction conditions. Preferred bulky amines include N,N-diisopropylethylamine (DIEA) and N-ethyldicyclohexylamine. The amount of bulky amine added is generally from about 1 to 10 equivalents, preferably 3 to 8 equivalents, more preferably 5 to 6 equivalents. The reaction is generally ran at temperatures from about room temperature (25°C) to about -20°C. However, Applicants discovered that lower temperatures (from about 0°C to about -20°C) further enhance the formation of monoamides at residue 3. The ratio of amidation at residue 3 vs. residue 8 increased as much as 20:1 by adding a bulky amine and lowering the temperature of the reaction.

However, it will be understood by those skilled in the art that the lower temperature limit will depend upon the solubility of the reactive components.

Once the acid group(s) are modified, then the amino protecting groups (at positions 2, 4 and 5) may be removed using standard procedures appropriate for the specific protecting group used. For example, CBZ groups are removed by hydrogenation in the presence of a hydrogenation catalyst (e.g., 10% Pd/C). When the amino protecting group is allyloxycarbonyl, then the protecting group may be removed using tributyltinhydride and triphenylphosphine palladium dichloride. This particular protection/deprotection scheme has the advantage of reducing the potential for hydrogenating the vinyl group of the Z-Dhb unit of the pseudomycin structure.

As discussed earlier, pseudomycins are natural products isolated from the bacterium Pseudomonas syringae that have been characterized as lipodepsinonapetpides containing a cyclic peptide portion closed by a lactone bond and including the unusual amino acids 4-chlorothreonine (ClThr), 3-hydroxyaspartic acid (HOAsp), 2,3-dehydro-2-aminobutyric acid (Dhb), and 2,4-diaminobutyric acid (Dab). Methods for growth of various strains of P. syringae to produce the different pseudomycin analogs (A, A', B, B', C, and C') are described below and described in more detail in PCT Patent

Application Serial No. PCT/US00/08728 filed by Hilton, et al. on April 14, 2000 entitled "Pseudomycin Production by Pseudomonas Syringae," incorporated herein by reference, PCT Patent Application Serial No. PCT/US00/08727 filed by Kulanthaivel, et al. on April 14, 2000 entitled "Pseudomycin Natural Products," incorporated herein by reference, and U.S. Patent Nos. 5,576,298 and 5,837,685, each of which are incorporated herein by reference.

Isolated strains of P. syringae that produce one or more pseudomycins are known in the art. Wild type strain MSU 174 and a mutant of this strain generated by transposon mutagenesis, MSU 16H are described in U.S. Patent Nos. 5,576,298 and 5,837,685; Harrison, et al., "Pseudomycins, a family of novel peptides from Pseudomonas syringae possessing broad-spectrum antifungal activity," J. Gen. Microbiology, 137, 2857-2865 (1991); and Lamb et al., "Transposon mutagenesis and tagging of fluorescent pseudomonas: Antimycotic production is necessary for control of Dutch elm disease," Proc. Natl. Acad. Sci. USA, 84, 6447-6451 (1987).

A strain of P. syringae that is suitable for production of one or more pseudomycins can be isolated from environmental sources including plants (e.g., barley plants, citrus plants, and lilac plants) as well as, sources such as soil, water, air, and dust. A preferred stain is isolated

from plants. Strains of P. syringae that are isolated from environmental sources can be referred to as wild type. As used herein, "wild type" refers to a dominant genotype which naturally occurs in the normal population of P. syringae (e.g., strains or isolates of P. syringae that are found in nature and not produced by laboratory manipulation). Like most organisms, the characteristics of the pseudomycin-producing cultures employed (P. syringae strains such as MSU 174, MSU 16H, MSU 206, 25-B1, 7H9-1) are subject to variation. Hence, progeny of these strains (e.g., recombinants, mutants and variants) may be obtained by methods known in the art.

P. syringae MSU 16H is publicly available from the American Type Culture Collection, Parklawn Drive, Rockville, MD, USA as Accession No. ATCC 67028. P. syringae strains 25-B1, 7H9-1, and 67 H1 were deposited with the American Type Culture Collection on March 23, 2000 and were assigned the following Accession Nos.:

25-B1	Accession No. PTA-1622
7H9-1	Accession No. PTA-1623
67 H1	Accession No. PTA-1621

Mutant strains of *P. syringae* are also suitable for production of one or more pseudomycins. As used herein, "mutant" refers to a sudden heritable change in the phenotype of a strain, which can be spontaneous or induced

by known mutagenic agents, such as radiation (e.g., ultraviolet radiation or x-rays), chemical mutagens (e.g., ethyl methanesulfonate (EMS), diepoxyoctane, N-methyl-N-nitro-N'-nitrosoguanine (NTG), and nitrous acid), site-specific mutagenesis, and transposon mediated mutagenesis. Pseudomycin-producing mutants of *P. syringae* can be produced by treating the bacteria with an amount of a mutagenic agent effective to produce mutants that overproduce one or more pseudomycins, that produce one pseudomycin (e.g., pseudomycin B) in excess over other pseudomycins, or that produce one or more pseudomycins under advantageous growth conditions. While the type and amount of mutagenic agent to be used can vary, a preferred method is to serially dilute NTG to levels ranging from 1 to 100 µg/ml. Preferred mutants are those that overproduce pseudomycin B and grow in minimal defined media.

Environmental isolates, mutant strains, and other desirable strains of *P. syringae* can be subjected to selection for desirable traits of growth habit, growth medium nutrient source, carbon source, growth conditions, amino acid requirements, and the like. Preferably, a pseudomycin producing strain of *P. syringae* is selected for growth on minimal defined medium such as N21 medium and/or for production of one or more pseudomycins at levels greater than about 10 µg/ml. Preferred strains exhibit the

characteristic of producing one or more pseudomycins when grown on a medium including three or fewer amino acids and optionally, either a lipid, a potato product or combination thereof.

Recombinant strains can be developed by transforming the *P. syringae* strains, using procedures known in the art. Through the use of recombinant DNA technology, the *P. syringae* strains can be transformed to express a variety of gene products in addition to the antibiotics these strains produce. For example, one can modify the strains to introduce multiple copies of the endogenous pseudomycin-biosynthesis genes to achieve greater pseudomycin yield.

To produce one or more pseudomycins from a wild type or mutant strain of P. syringae, the organism is cultured with agitation in an aqueous nutrient medium including an effective amount of three or fewer amino acids, preferably glutamic acid, glycine, histidine, or a combination thereof. Alternatively, glycine is combined with one or more of a potato product and a lipid. Culturing is conducted under conditions effective for growth of *P. syringae* and production of the desired pseudomycin or pseudomycins. Effective conditions include temperatures from about 22°C to about 27°C, and a duration of about 36 hours to about 96 hours. Controlling the concentration of oxygen in the medium during culturing of *P. syringae* is advantageous for

production of a pseudomycin. Preferably, oxygen levels are maintained at about 5 to 50% saturation, more preferably about 30% saturation. Sparging with air, pure oxygen, or gas mixtures including oxygen can regulate the concentration of oxygen in the medium.

Controlling the pH of the medium during culturing *of P. syringae* is also advantageous. Pseudomycins are labile at basic pH, and significant degradation can occur if the pH of the culture medium is above about 6 for more than about 12 hours. Preferably, the pH of the culture medium is maintained between 6 and 4. *P. syringae* can produce one or more pseudomycins when grown in batch culture. However, fed-bath or semi-continuous feed of glucose and optionally, an acid or base (e.g., ammonium hydroxide) to control pH, enhances production. Pseudomycin production can be further enhanced by using continuous culture methods in which glucose and ammonium hydroxide are fed automatically.

Choice of *P. syringae* strain can affect the amount and distribution of pseudomycin or pseudomycins produced. For example, strains MSU 16H and 67 H1 each produce predominantly pseudomycin A, but also produce pseudomycin B and C, typically in ratios of 4:2:1. Strain 67 H1 typically produces levels of pseudomycins about three to five fold larger than are produced by strain MSU 16H. Compared to strains MSU 16H and 67 H1, strain 25-B1 produces more

pseudomycin B and less pseudomycin C. Strain 7H9-1 are distinctive in producing predominantly pseudomycin B and larger amount of pseudomycin B than other strains. For example, this strain can produce pseudomycin B in at least a ten fold excess over either pseudomycin A or C.

Each pseudomycin, pseudomycin intermediate and mixtures can be detected, determined, isolated, and/or purified by any variety of methods known to those skilled in the art. For example, the level of pseudomycin activity in a broth or in an isolate or purified composition can be determined by antifungal action against a fungus such as Candida and can be isolated and purified by high performance liquid chromatography.

Alternatively, the amido or ester derivative can be formed from an N-acyl semi-synthetic compound. Semi-synthetic pseudomycin compounds may be synthesized by exchanging the N-acyl group on the L-serine unit. Examples of various N-acyl derivatives are described in PCT Patent Application Serial No. _____, Belvo, et al., filed evendate herewith entitled "Pseudomycin N-Acyl Side-Chain Analogs" and incorporated herein by reference. In general, four synthetic steps are used to produce the semi-synthetic compounds from naturally occurring pseudomycin compounds: (1) selective amino protection; (2) chemical or enzymatic deacylation of the N-acyl side-chain; (3) reacylation with a

different side-chain; and (4) deprotection of the amino groups. The aspartic acid and/or hydroxyaspartic acid units can be modified prior to deprotecting the amino groups.

The deacylation of an N-acyl group having a gamma or delta hydroxylated side chain (e.g., 3,4-dihydroxytetradeconoate) may be accomplished by treating the amino-protected pseudomycin compound with acid in an aqueous solvent. Suitable acids include acetic acid and trifluoroacetic acid. A preferred acid is trifluoroacetic acid. If trifluoroacetic acid is used, the reaction may be accomplished at or near room temperature. However, when acetic acid is used the reaction is generally ran at about 40°C. Suitable aqueous solvent systems include acetonitrile, water, and mixtures thereof. Organic solvents accelerate the reaction; however, the addition of an organic solvent may lead to other by-products. Pseudomycin compounds lacking a delta or gamma hydroxy group on the side chain (e.g., Pseudomycin B and C') may be deacylated enzymatically. Suitable deacylase enzymes include Polymyxin Acylase (164-16081 Fatty Acylase (crude) or 161-16091 Fatty Acylase (pure) available from Wako Pure Chemical Industries, Ltd.), or ECB deacylase. The enzymatic deacylation may be accomplished using standard deacylation procedures well known to those skilled in the art. For example, general procedures for using polymyxin acylase may be found in

Yasuda, N., et al, *Agric. Biol. Chem.*, 53, 3245 (1989) and Kimura, Y., et al., *Agric. Biol. Chem.*, 53, 497 (1989).

The deacylated product (also known as the pseudomycin nucleus) is reacylated using the corresponding acid of the desired acyl group in the presence of a carbonyl activating agent. "Carbonyl activating group" refers to a substituent of a carbonyl that promotes nucleophilic addition reactions at that carbonyl. Suitable activating substituents are those which have a net electron withdrawing effect on the carbonyl. Such groups include, but are not limited to, alkoxy, aryloxy, nitrogen containing aromatic heterocycles, or amino groups (e.g., oxybenzotriazole, imidazolyl, nitrophenoxy, pentachlorophenoxy, N-oxysuccinimide, N,N'-dicyclohexylisoure-O-yl, and N-hydroxy-N-methoxyamino); acetates; formates; sulfonates (e.g., methanesulfonate, ethanesulfonate, benzenesulfonate, and *p*-tolylsulfonate); and halides (e.g., chloride, bromide, and iodide).

A variety of acids may be used in the acylation process. Suitable acids include aliphatic acids containing one or more pendant aryl, alkyl, amino(including primary, secondary and tertiary amines), hydroxy, alkoxy, and amido groups; aliphatic acids containing nitrogen or oxygen within the aliphatic chain; aromatic acids substituted with alkyl, hydroxy, alkoxy and/or alkyl amino groups; and

heteroaromatic acids substituted with alkyl, hydroxy, alkoxy and/or alkyl amino groups.

Alternatively, a solid phase synthesis may be used where a hydroxybenzotriazole-resin (HOBt-resin) serves as the coupling agent for the acylation reaction.

The acid-modification of the protected N-acyl semi-synthetic compound is then accomplished by reacting at least one of the pendant carboxyl groups attached to the aspartic or hydroxyaspartic peptide units of the N-acyl modified semi-synthetic pseudomycin compound to form the desired amide or ester linkage(s). The protecting groups are then removed as described earlier.

The pseudomycin compound may be isolated and used per se or in the form of its pharmaceutically acceptable salt or solvate. The term "pharmaceutically acceptable salt" refers to non-toxic acid addition salts derived from inorganic and organic acids. Suitable salt derivatives include halides, thiocyanates, sulfates, bisulfates, sulfites, bisulfites, arylsulfonates, alkylsulfates, phosphonates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphonates, alkanoates, cycloalkylalkanoates, arylalkonates, adipates, alginates, aspartates, benzoates, fumarates, glucoheptanoates, glycerophosphates, lactates, maleates, nicotinates, oxalates, palmitates, pectinates, picrates, pivalates, succinates, tartarates, citrates,

camphorates, camphorsulfonates, digluconates, trifluoroacetates, and the like.

The term "solvate" refers to an aggregate that comprises one or more molecules of the solute (i.e., pseudomycin compound) with one or more molecules of a pharmaceutical solvent, such as water, ethanol, and the like. When the solvent is water, then the aggregate is referred to as a hydrate. Solvates are generally formed by dissolving the compound in the appropriate solvent with heat and slowing cooling to generate an amorphous or crystalline solvate form.

The active ingredient (i.e., pseudomycin compound) is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient, physician or veterinarian an elegant and easy to handle product. Formulations may comprise from 0.1% to 99.9% by weight of active ingredient, more generally from about 10% to about 30% by weight.

As used herein, the term "unit dose" or "unit dosage" refers to physically discrete units that contain a predetermined quantity of active ingredient calculated to produce a desired therapeutic effect. When a unit dose is administered orally or parenterally, it is typically provided in the form of a tablet, capsule, pill, powder packet, topical composition, suppository, wafer, measured

units in ampoules or in multidose containers, etc. Alternatively, a unit dose may be administered in the form of a dry or liquid aerosol which may be inhaled or sprayed.

The dosage to be administered may vary depending upon the physical characteristics of the animal, the severity of the animal's symptoms, the means used to administer the drug and the animal species. The specific dose for a given animal is usually set by the judgment of the attending physician or veterinarian.

Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the active ingredient is being applied. The formulations may also include wetting agents, lubricating agents, surfactants, buffers, tonicity agents, bulking agents, stabilizers, emulsifiers, suspending agents, preservatives, sweeteners, perfuming agents, flavoring agents and combinations thereof.

A pharmaceutical composition may be administered using a variety of methods. Suitable methods include topical (e.g., ointments or sprays), oral, injection and inhalation.

The particular treatment method used will depend upon the type of infection being addressed.

In parenteral iv applications, the formulations are typically diluted or reconstituted (if freeze-dried) and further diluted if necessary, prior to administration. An example of reconstitution instructions for the freeze-dried product are to add ten ml of water for injection (WFI) to the vial and gently agitate to dissolve. Typical reconstitution times are less than one minute. The resulting solution is then further diluted in an infusion solution such as dextrose 5% in water (D5W), prior to administration.

Pseudomycin compounds have been shown to exhibit antifungal activity such as growth inhibition of various infectious fungi including Candida spp. (i.e., *C. albicans, C. parapsilosis, C. krusei, C. glabrata, C. tropicalis,* or *C. lusitaniaw*); Torulopus spp.(i.e., *T. glabrata*); Aspergillus spp. (i.e., *A. fumigatus*); Histoplasma spp. (i.e., *H. capsulatum*); Cryptococcus spp. (i.e., *C. neoformans*); Blastomyces spp. (i.e., *B. dermatitidis*); Fusarium spp.; Trichophyton spp., *Pseudallescheria boydii, Coccidioides immits, Sporothrix schenckii*, etc.

Consequently, the compounds and formulations of the present invention are useful in the preparation of medicaments for use in combating either systemic fungal

infections or fungal skin infections. Accordingly, a method is provided for inhibiting fungal activity comprising contacting the pseudomycin compound of the present invention with a fungus. A preferred method includes inhibiting *Candida albicans* or *Aspergillus fumigatus* activity. The term "contacting" includes a union or junction, or apparent touching or mutual tangency of a compound of the invention with a fungus. The term does not imply any further limitations to the process, such as by mechanism of inhibition. The methods are defined to encompass the inhibition of fungal activity by the action of the compounds and their inherent antifungal properties.

A method for treating a fungal infection which comprises administering an effective amount of a pharmaceutical formulation of the present invention to an animal host in need of such treatment is also provided. A preferred method includes treating a *Candida albicans* or *Aspergillus fumigatus* infection. The term "effective amount" refers to an amount of active compound which is capable of inhibiting fungal activity. The dose administered will vary depending on such factors as the nature and severity of the infection, the age and general health of the host, the tolerance of the host to the antifungal agent and species of the host. The particular dose regimen likewise may vary according to these factors.

The medicament may be given in a single daily dose or in multiple doses during the day. The regimen may last from about 2-3 days to about 2-3 weeks or longer. A typical daily dose (administered in single or divided doses) contains a dosage level between about 0.01 mg/kg to 100 mg/kg of body weight of an active compound. Preferred daily doses are generally between about 0.1 mg/kg to 60 mg/kg and more preferably between about 2.5 mg/kg to 40 mg/kg. The host may be any animal including humans, companion animals (e.g., dogs, cats and horses), food-source animals (e.g., cows, pigs, sheep and poultry), zoo animals, marine animals, birds and other similar animal species.

EXAMPLES

Unless indicated otherwise, all chemicals can be acquired from Aldrich Chemical (Milwaukee, WI). The following abbreviations are used through out the examples to represent the respective listed materials:

ACN - acetonitrile

TFA - trifluoroacetic acid

DMF - dimethylformamide

EDCI - 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride

BOC = t-butoxycarbonyl, $(CH_3)_3C-O-C(O)-$

CBZ = benzyloxycarbonyl, $C_6H_5CH_2-O-C(O)-$

PyBOP = benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate

TBTU = *o*-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium

tetrafluoroborate

DIEA = N,N-diisopropylethylamine

HPLC Conditions

Unless indicated otherwise, analytical reverse-phase HPLC work was done using the Waters 600E systems equipped with Waters μBondapak (C18, 3.9 X 300 mm) column. The eluent used was 65:35 acetonitrile/0.1% aqueous TFA solvent system to 100% acetonitrile over 20 minutes with a flow rate of 1.5 ml/minute and using UV detection at 230 nm.

Preparative HPLC work was performed with a Waters Prep 2000 system using Dynamax 60 angstrom C18 column and identical solvent systems as used in the analytical HPLC system but with a flow rate of 40 ml/min.

Biological Analysis

Detection and Quantification of Antifungal Activity:

Antifungal activity was determined *in vitro* by obtaining the minimum inhibitory concentration (MIC) of the compound using a standard agar dilution test or a disc-diffusion test. A typical fungus employed in testing antifungal activity is *Candida albicans*. Antifungal activity is considered significant when the test sample (50 μl) causes 10-12 mm diameter zones of inhibition on *C. albicans* x657 seeded agar plates.

Tail Vein Toxicity:

Mice were treated intravenously (IV) through the lateral tail vein with 0.1 ml of testing compound (20 mg/kg) at 0, 24, 48 and 72 hours. Two mice were included in each group. Compounds were formulated in 5.0% dextrose and sterile water for injection. The mice were monitored for 7 days following the first treatment and observed closely for signs of irritation including erythema, swelling, discoloration, necrosis, tail loss and any other signs of adverse effects indicating toxicity.

The mice used in the study were outbred, male ICR mice having an average weight between 18-20 g (available from Harlan Sprangue Dawley, Indianapolis, IN).

General Procedures

CBZ-Protected Pseudomycin: General procedures used to protect the pendant amino groups at positions 2, 4 and 5 of Pseudomycin A, A', B, B', C or C' with CBZ.

Dissolve/suspend pseudomycin compound (R^1=H) in DMF (20 mg/ml, Aldrich Sure Seal). While stirring at room temperature add *N*-(Benzyloxycarbonyloxy)succinimide (6 eq). Allow to stir at room temperature for 32 hours. Monitor reaction by HPLC (4.6x50 mm, 3.5 µm, 300-SB, C8, Zorbax column). Concentrate reaction to 10 ml on high vacuum rotovap at room temperature. Put material in freezer until ready to prep by chromatography. Reverse phase preparative

HPLC yields an amorphous, white solid after lyophilization (R^1 = CBZ in structure II below).

Alloc-Protected Pseudomycin: General procedures used to protect the pendant amino groups at positions 2, 4 and 5 of Pseudomycin A, A', B, B', C or C' with Alloc.

Diallyl pyrocarbonate (558 mg, 3.0 mmol) was added to a solution of Pseudomycin A (1.22 g, 1.0 mmol) in 600 ml DMF. The reaction was stirred at room temperature overnight. The solvent was removed in vacuo to afford an oily residue which was washed with ether three times. The oily residue was redissolved in a mixture of water and ACN (~1:1) and lyophilized to provide an alloc-protected psuedomycin A compound in 90% yield.

The alloc-protected pseudomycin B compound was prepared using the same procedures in 90% yield (R^1 = alloc in structure II below).

General procedures used to remove CBZ protecting groups at position 2, 4 and 5 by hydrogenation.

Dissolve CBZ-protected acylated-derivative in a cold 1% to 10% acetic/methanol solution (5 mg/ml) and add an equivalent amount of 10% Pd/C. Charge the reaction with hydrogen by degassing reaction and replacing volume with H_2 ,4-7 times. Allow reaction to proceed at room temperature.

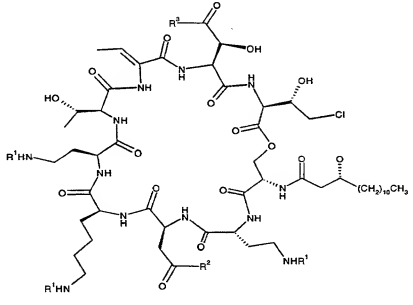
Monitor the reaction by HPLC every hour until starting material is consumed. When the reaction is complete, remove balloon and filter reaction with 0.45 μm filter disk (Acrodisk GHP, GF by Gelman). Concentrate to about 1/10th volume and prep by HPLC. Lyophilize fractions containing product.

General procedures used to remove Alloc protecting groups at position 2, 4 and 5 with tributyltinhydride and triphenylphosphine palladium dichloride.

Acetic acid (1 ml) was added to a suspension of alloc-protected pseudomycin B (0.05 mmol) in 5 ml methylene chloride. After degassing under vacuum, the solution was treated with 6.0 mg $PdCl_2(PPH_3)_2$ (0.008 mmol) and 0.40 ml tri-*n*-butyltin hydride (1.5 mmol)at room temperature for 2 hours. The solvent was evaporated *in vacuo* and the residue dissolved in water/ACN (~1:1) and filtered. The resulting solution was purified by preparative HPLC to afford the desired pseudomycin B compound in 93% yield. Alternatively, 5 ml tetrahydrofuran and 0.1 ml acetic acid may be used as the solvent instead of 5 ml methylene chloride and 1.0 ml acetic acid.

The following structure II will be used to describe the products observed in Examples 1 through 27. Although a specific pseudomycin natural product (pseudomycin B) was

used in the Examples below, those skilled in the art will appreciate that other pseudomycin natural products or semi-synthetic derivatives may be used as starting materials.



II

Examples 1-3 illustrate the formation of bis-esters at residues 3 and 8.

Example 1

Synthesis of Bis-Ethyl ester 1-1:

R^1 = H
R^2 = $-OCH_2CH_3$
R^3 = $-OCH_2CH_3$

1-1

A 50 ml round bottom flask was charged with 10 ml of absolute ethanol and CBZ-protected pseudomycin B(251.7 mg, 0.156 mmol). To this mixture was added ~ 1 ml of acidified ethanol (previously acidified using HCl gas) and the reaction was allowed to stir at room temperature overnight.

The solvent was then removed *in vacuo* and the residue was carried on to the next step without further purification by dissolving it in a solution of 10 ml MeOH/1.5 ml glacial AcOH. Standard hydrogenolysis using 249.7 mg of 10% Pd/C for 30 minutes, removal of the catalyst via filtration and purification via preparatory HPLC led to Compound **1-1** (120.9 mg) after lyophilization. MS (Ionspray) calcd for $C_{55}H_{96}ClN_{12}O_{19}$ $(M+H)^+$ 1264.89, found 1264.3.

The mono-esters may be isolated by following the reaction carefully by HPLC. The reaction is stopped at the appropriate time when the ratio of starting material: mono ester(s): bis ester is greatest. The methodology remains the same. The resulting mixture of mono esters is isolated where some ester is formed on the aspartic acid residue and some on the hydroxy aspartic acid residue. This mixture of CBZ-protected, mono esters is hydrogenated using standard methodology to yield a mixture of mono ethyl esters of Pseudomycin B.

Compounds 1-2 and 1-3 were synthesized using the same procedures described above.

R = -H
R2 = $-OCH_3$
R3 = $-OCH_3$

1-2

R = -H
R^2 = $-OCH(CH_3)_2$
R^3 = $-OCH(CH_3)_2$

1-3

Example 2 illustrates the synthesize of bis-esters using basic conditions.

Example 2

Synthesis of Bis-propyl ester 2-1:

$R = -H$
$R^2 = -OCH_2CH_2CH_3$
$R^3 = -OCH_2CH_2CH_3$

2-1

CBZ-protected pseudomycin B (247.3 mg, 0.154 mmol) was dissolved in 5 ml DMF. A large excess of propyl iodide and an excess of $NaHCO_3$ were then added. The reaction was allowed to stir for 10 h at room temperature. Purification via preparatory HPLC followed by lyophilization provided 147.6 mg of the protected bis ester. Hydrogenolyis of this compound under standard condition using 149.3 mg of 10% Pd/C yielded 78.9 mg of Compound **2-1** after HPLC purification and lyophilization.

Example 3

$R = -H$
$R^2 = -O(CH_2)_4CH_3$
$R^3 = -OH$

3-1

$R = -H$
$R^2 = -OH$
$R^3 = -O(CH_2)_4CH_3$

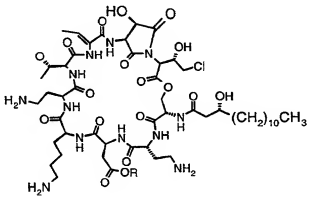
3-2

CBZ-protected pseudomycin B (282.3 mg, 0.175 mmol) was dissolved in 5 ml DMF. A large excess of *n*-pentyl iodide and an excess of $NaHCO_3$ were then added. The reaction was allowed to stir for 10 h at room temperature. Purification via preparatory HPLC followed by lyophilization provided

49.1 mg of the mixture of protected mono pentyl esters. Hydrogenolyis of this mixture under standard condition using 47.3 mg of 10% Pd/C yielded 30.6 mg of Compounds **3-1 and 3-2** after HPLC purification and lyophilization.

R = -H	R = -H	R = -H
R^2 = $-O(CH_2)_3CH_3$	R^2= $-O(CH_2)_3CH_3$	R^2 = -OH
R^3 = $-O(CH_2)_3CH_3$	R^3 = -OH	R^3 = $-O(CH_2)_3CH_3$
3-3	**3-4**	**3-5**

Substitution of the propyl iodide with n-butyl iodide afforded the bis-butyl ester (**3-3**), a mixture of mono esters (**3-4** + **3-5**) and a mixture of mono ester + the following cyclic imide compound **3-6**:



3-6

Example 4

Synthesis of cyclopentylmethyl ester 4-1:

R = -H
R^2 = $-OCH_2$(cyclopentyl)
R^3 = -OH

4-1

CBZ-protected pseudomycin B, a large excess of p-toluenesulfonic acid and cyclopentanemethanol are mixed and allowed to stir overnight. An additional 10 equivalents of alcohol was added the next day. The CBZ-protected ester was isolated via preparatory HPLC and then hydrogenated using standard methodology to produce Compound 4-1.

Each of the compounds synthesized in Examples 1-4 showed measurable activity against *Candida Albicans*, *Cryptococcus neoformans*, *Aspergillus Fumigatus*, *Candida Parapsilosis*, or *Histoplasma capsulatum*. However, the following basic trends in activity were observed based on the compounds synthesized. Simple esters (bis-methyl, bis-ethyl and mono-ethyl) were active and efficacious; however, the larger esters exhibited less efficacy (e.g., propyl esters and larger). ADME has shown that Compounds **1-1** and **2-1** quickly cleave to the parent pseudomycin B compound.

Examples 5-11 illustrate the synthesis of amide derivatives at residue 3.

Example 5

Synthesis of Compound 5-1:

$R = -H$
$R^2 = -NH_2$
$R^3 = -OH$

5-1

CBZ-protected pseudomycin B (1.12 g) and 224 mg TBTU, 0.56 ml DIEA and 1.0 g deprotected rink amide resin (4-(2',4'-dimethoxyphenyl-aminomethyl)-phenoxy resin, available from Advance ChemTech, Inc., Louisville, KY) were mixed for 3 days. The mixture was filtered and the resin washed 3x with DMF and 3x with dichloromethane. The resin was treated with 5% water in 1:1 TFA/CH_2Cl_2 for 3 hours. The mixture was filtered and the resin washed 3x with TFA. The filtrate was collected and concentrated in vacuo. Upon purification by HPLC, 60 mg (5.3%) of the CBZ-protected amido product was isolated.

The protected amido compound (60 mg) was dissolved in 6 ml of 1% AcOH in methanol and 60 mg of 10% Pd/C was added. The mixture was stirred for 30 minutes under hydrogen at room temperature. After filtering, the solution was concentrated in vacuo. The residue was dissolved in 50% ACN/water and lyophilized to yield 45 mg (90%) yield of Compound **5-1**.

Example 6

Synthesis of Compound 6-1:

R = -H
R^2 = -NH(cyclopropyl)
R^3 = -OH

6-1

CBZ-protected pseudomycin B (400 mg, 0.25 mmol) is dissolved in 4 ml dry DMF. TBTU (79 mg, 0.25 mmol), DIEA (200 µl, 6 equivalents) and cyclopropylamine (14.2 mg, 0.25 mmol) were added sequentially. The reaction was stirred at room temperature under nitrogen while being monitored by HPLC. Upon completion the reaction was concentrated *in vacuo*. The crude product purified by preparative HPLC. Lyophilization yielded 209.2 mg (51.1%) of a colorless powder.

The 3-amido compound (279.1 mg, 0.169 mmol) was hydrogenated under hydrogen balloon catalyzed by 10% Pd/C in 1% HOAc/MeOH for 45 minutes. The reaction was filtered and concentrated *in vacuo*. The residue was picked up in a 1:1 mixture of water:ACN and then lyophilized to give 208.3 mg (98.6%) of a colorless powder. The structure was verified by H^1-NMR.

Compound **6-1** can also be made from the Alloc-protected pseudomycin B using the following procedures.

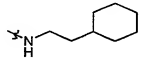
1-Hydroxybenzotriazole hydrate (136 mg, 1.0 mmol) and EDCI (211 mg, 1.1 mmol) was added to a solution of alloc-protected pseudomycin B (730 mg, 0.50 mmol) in 7 ml of DMF. After stirring overnight, cyclopropylamine (85.6 mg, 1.5 mmol) was added. The progress of the reaction was monitored by HPLC. Upon completion, the alloc-protected pseudomycin

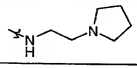
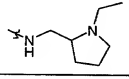
derivative (334 mg, 50% yield) was isolated via preparative HPLC and lyophilization.

The alloc-protected intermediate (117 mg, 0.078 mmol) was dissolved in 15 ml of methylene chloride and 1 ml of acetic acid. After degassing the reaction mixture with dry nitrogen, 30 mg of $(PPh_3)_2PdCl_2$ and 1 ml of tributyltinhydride was added to the mixture. The progress of the reaction was monitored by HPLC. Upon completion, the reaction mixture was purified by reverse phase preparative HPLC to provide 88 mg (91% yield) of Compound **6-1**.

Table I below lists other 3-amido derivatives that were synthesized using the same general procedures described above using the appropriate corresponding amine starting material.

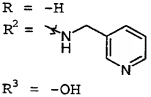
Table I

Example #	R^1	R^2	R^3
6-2	-H	$-NHCH_3$	-OH
6-3	-H	$-NHCH_2CH_3$	-OH
6-4	-H	$-NHCH_2CF_3$	-OH
6-5	-H	$-NH(CH_2)_2CH_3$	-OH
6-6	-H	$-NHCH_2(CH_3)_2$	-OH
6-6	-H	-NH(cyclopropyl)	-OH
6-7	-H	$-NHCH_2CH=CH_2$	-OH
6-8	-H	$-NH(CH_2)_4CH_3$	-OH
6-9	-H	$-NHCH(CH_3)(CH_2)_2CH_3$	-OH
6-10	-H	$-NH(CH_2)_5CH_3$	-OH
6-11	-H	-NH(cyclohexyl)	-OH
6-12	-H	$-NH(CH_2)_6CH_3$	-OH
6-13	-H	$-NH(CH_2)_7CH_3$	-OH
6-14	-H	$-NH(CH_2)_8CH_3$	-OH
6-15	-H	$-NH(CH_2)_9CH_3$	-OH
6-16	-H		-OH
6-17	-H	$-NH(CH_2)_2N(CH_3)_2$	-OH

6-18	-H	$-NH(CH_2)_2N(CH_2CH_3)_2$	-OH
6-19	-H	$-NH(CH_2)_3N(CH_3)_2$	-OH
6-20	-H	$-NH(CH_2)_3N(CH_2CH_3)_2$	-OH
6-21	-H	$-NH(CH_2)_4N(CH_3)_2$	-OH
6-22	-H	$-NH(CH_2)_6N(CH_3)_2$	-OH
6-23	-H	$-NH(CH_2)_7N(CH_3)_2$	-OH
6-24	-H		-OH
6-25	-H		-OH

Example 7

Synthesis of 3-amido compound 7-1:



7-1

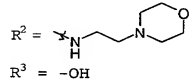
In a 500 mL oven dried round bottom flask, CBZ-protected Pseudomycin B(0.5 g, 0.311mmol) was dissolved in 25 mL of DMF. To this solution was added TBTU(0.2 g, 0.622 mmol), 3-(aminomethyl)pyridine(0.067 g, 0.622mmol), and N-ethyldicyclohexylamine(0.391 g, 1.87 mmol). The solution was stirred for three hours and then concentrated down. The product was isolated by reverse-phase preparatory HPLC, and lyophilized to yield, (96 mg, 18% yield) CBZ-protected amide. The deprotection of the CBZ groups was performed by adding slowly an equivalent mass of 10%Pd/C to a cold 1%

acetic/methanol solution of CBZ-protected amide. The solution was allowed to warm to rt and stirred rapidly for 3.5 hours under 1 atm H_2. After removal of the catalyst via filtration, purification on reverse phase HPLC and lyophilization yielded 40 mg , 55% yield of Compound **7-1**. MS data Calculated for C57 H93 Cl N14 O18 Mol. Wt. = 1296.6 Found ES+ 1297.15, ES- 1294.95

Example 8

Synthesis of 3-amido compound 8-1:

R = -H



R^3 = -OH

8-1

The same general procedures as described in Example 7 may be used. When no base is added, a mixture of 8 and 3 amido substituted compounds are observed.

Example 9

Synthesis of 3-amido compound 9-1:

R = -H
R^2 = -NH(benzyl)
R^3 = -OH

9-1

R = -H
R^2 = -NH(benzyl)
R^3 = -NH(benzyl)

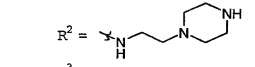
9-2

The same general procedures as described in Example 7 may be used. When no base is added, a mixture of Compounds 9-1 and 9-2 are observed.

Example 10

Synthesis of 3-amido compound 10-1:

R = -H



R^3 = -OH

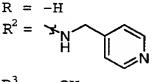
10-1

The same general procedures as described in Example 7 are used to synthesize Compound 10-1 using the appropriate corresponding amine starting material.

Example 11

Synthesis of 3-amido compound 11-1:

R = -H



R^3 = -OH

11-1

The same general procedures as described in Example 7 are used to synthesize Compound 11-1 using 4-(aminomethyl) pyridine as the amine starting material.

Example 12

Synthesis of 3-amido Compound 12-1:

R = -H

R^2 = $-N(CH_3)_2$

R^3 = -OH

12-1

CBZ-protected pseudomycin B (260 mg, 0.16 mmol), 51.8 mg TBTU and 152 µl DIEA were dissolved in 3 ml DMF and 320 ml dimethylamine (0.16 mmol) in THF (2 molar solution). The reaction was stirred at room temperature for 20 minutes and the then purified via HPLC. The product was lyophilized to give 172 mg (66% yield) of the desired CBZ-protected amide.

The CBZ-protected amide was hydrogenated using the general procedure described above to provide Compound **12-1**.

Example 13 illustrates the synthesis of pseudomycin compounds where the carboxylic acid group is reacted with a variety of amino acid alkyl esters.

Example 13

Synthesis of 3-amido Compound 13-1:

$R = -H$
$R^2 = -NHCH(CO_2CH_3)CH_2CH_2CH_2CH_2NH_2$
$R^3 = -OH$

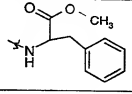
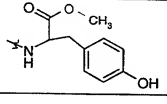
13-1

CBZ-protected Lysine methyl ester (164 mg, 0.49 mmol) was added to a solution of CBZ-protected pseudomycin B (800 mg, 0.49 mmol), TBTU (158 mg, 0.49 mmol) and 400 ml DIEA (2.51 mmol) in 8 ml DMF. The reaction was allowed to stir at room temperature for 20 minutes and then purified via HPLC to yield 260 mg (32% yield) of the CBZ-protected amide.

The CBZ-protected amide was hydrogenated using the general procedures described above to produce Compound **13-1**.

The compounds 13-2 through 13-4 listed in Table II may be synthesized using the same general procedures as described above using the appropriate corresponding aminoacid ester.

Table II

Example #	R^1	R^2	R^2
13-2	-H	$-NHCH_2CO_2CH_3$	-OH
13-3	-H		-OH
13-4	-H		-OH

Examples 14-16 illustrate the synthesis of amide derivatives at residue 8.

Example 14

Synthesis of 8-amido Compound 14-1:

R = -H
R^2 = -OH
R^3 = $-NH_2$

14-1

Compound 14-1 is synthesized using the same procedures as described for compound 6-1 using a rink amide resin with the exception that PyBOP is used as the coupling agent instead of TBTU.

Example 15

Synthesis of 8-amido Compound 15-1:

$R = -H$
$R^2 = -OH$
$R^3 = -NH(CH_2)_3CH_3$

15-1

n-Butyl amine (45.4 mg, 0.62 mmol) was added to a solution of CBZ-protected pseudomycin B (1000 mg, 0.62 mmol) and PyBop (323 mg, 0.62 mmol) dissolved in 10 ml of DMF. The reaction was stirred at room temperature for 1 hour and then purified via HPLC. The product was lyophilized to give 280 mg (27% yield) of the CBZ-protected amide.

The CBZ-protected amide (280 mg, 0.17 mmol) was hydrogenated under hydrogen catalyzed by 10% Pd/C in 1% acetic acid/methanol for 45 minutes. The reaction mixture was filtered and the solvent removed *in vacuo*. The residue was dissolved in 50% ACN in water and lyophilized to give 189 mg (89% yield) of Compound **15-1**.

The 8-amido compounds listed in Table III may be synthesized using the same general procedures described above using the appropriate corresponding amine starting material.

Table III

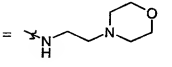
Example #	R^1	R^2	R^3
15-2	-H	-OH	$-NHCH_3$
15-3	-H	-OH	$-NHCH_2CH_3$
15-4	-H	-OH	$-NH(CH_2)_2CH_3$
15-5	-H	-OH	-NH(cyclopropyl)
15-6	-H	-OH	-NH(cyclobutyl)
15-7	-H	-OH	$-NHCH_2CH_2OH$
15-8	-H	-OH	$-NHCH_2CH_2N(CH_3)_2$
15-9	-H	-OH	$-NHCH_2CH_2CH_2N(CH_3)_2$

Example 16

Synthesis of 8-amido Compound 16-1:

R = -H

R^2 = -OH

R^3 = 

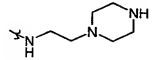
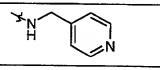
16-1

In a 100 ml round bottom flask, alloc-protected Pseudomycin B(0.25 g, 0.171 mmol) was dissolved in 25 ml of DMF. To this solution was added Pybop (0.089g, 0.171 mmol)and 4-(2-Aminoethyl)morpholine (0.022 g, 0.171 mmol). The solution was stirred rapidly overnight under 1 atm N_2. The solution was concentrated down, and the product was isolated by reverse-phase HPLC, and lyophilized to yield (140 mg, 0.089 mmol, 52%) alloc-protected Psuedomycin B Morpholine derivative. The deprotection of the alloc groups was performed by adding Bu_3SnH(0.648 g, 2.23 mmol), and $(Ph_3P)_2PdCl_2$(0.009g, 0.013 mmol) to a 1% acetic/

dichloromethane solution of alloc-protected Psuedomycin B Morpholine derivative (10 mg/mL). Reaction time was 30 minutes. Reaction was monitored by HPLC. The solution was concentrated down, and the product was isolated by reverse phase HPLC prep, and lyophilized to yield 38 mg, 32% of Compound 16-1. **MS data:** Calculated for C57 H99 Cl N14 O19 Mol. Wt. 1318.7 Found ES+ 1320.0, ES- 1318.0

The 8-amido compounds listed in Table IV were synthesized using the same general procedures described above using the appropriate corresponding amine starting material.

Table IV

Example #	R^1	R^2	R^3
16-2	-H	-OH	-NH(benzyl)
16-3	-H	-OH	
16-4	-H	-OH	

Each of the compounds synthesized in Examples 5-16 showed measurable activity against *Candida Albicans*, *Cryptococcus neoformans*, *Aspergillus Fumigatus*, *Candida Parapsilosis*, or *Histoplasma capsulatum*. However, the following basic trends in activity were observed based on the compounds synthesized.

When the 8-amido derivatives were assayed against *C. albicans*, several trends were apparent from the data. The *in vitro* potency decreases in the following order of R^3 substitution: $-NH_2$ > $-NHCH_3$ > $-NHCH_2CH_3$ > $-NH(CH_2)_2CH_3$ > $-NH(CH_2)_3CH_3$; $-NHCH_2CH_2N(CH_3)_2$ > $-NH(CH_2)_3N(CH_3)_2$; and -NH(GlyOMe) > -NH(PheOMe). In general, better activities were realized with amido groups having smaller alkyl groups. The free amide group was found to be the most active of the series. In addition, the cycloalkyl amides demonstrated better activity than the corresponding straight chain alkyl groups. Alkyl groups having a polar substitution on the end of the alkyl chain showed less activity than the corresponding natural product. Unlike the parent natural product, none of the 8-amido derivatives showed tail vein irritation.

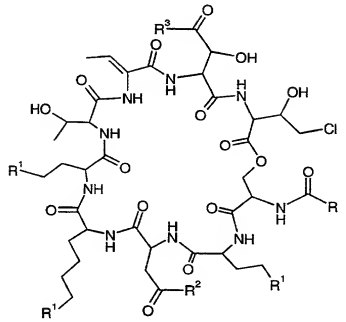
The 3-amido derivatives demonstrated a similar trend as observed with the 8-amido derivatives in comparison with the parent natural product (e.g., amide substituents at R^2 having shorter alkyl chains were more active than longer alkyl chains). Unlike the 8-amido derivatives, the 3-amido derivatives did not show a significant decrease in *in vitro* activity against *C. albicans* until the alkyl chain reached 7-carbons or longer (3-amido PSB compound where R^2 = $-NH(CH_2)_6CH_3$ had a MIC = 20 µg/ml) versus 4-carbons or longer for the 8-amido derivatives (8-amido PSB compound where R^3 =

$-NH(CH_2)_3CH_3$ had a MIC = 20 μg/ml). Most of the 3-amido derivatives tested showed an improvement in tail vein irritation. The exceptions being R^2 = -NH(*iso*-amyl), -NH(*n*-hexyl), $-NH(CH_2)_2N(CH_2CH_3)_2$, and $-NH(CH_2)_3N(CH_3)_2$.

Although formation of an amide bond at residues 3 and 8 demonstrated an improved toxicity profile in comparison with the corresponding natural product (Pseudomycin B), *in vivo* efficacy generally decreased.

WE CLAIM:

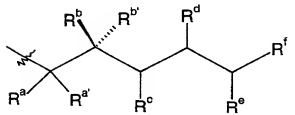
1. A pseudomycin compound having the following structure I



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a

double bond, or taken together with R^c forms a six-membered aromatic ring;

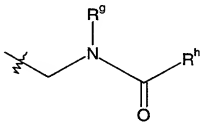
R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_8-C_{18} alkyl, or C_5-C_{11} alkoxy;

R is



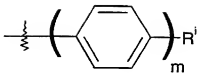
,

where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

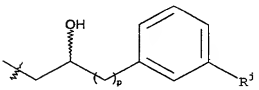
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

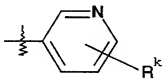
R is



where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is $-(CH_2)-NR^m-(C_{13}$-C_{18} alkyl), where R^m is H, $-CH_3$ or $-C(O)CH_3$;

R^1 is independently $-NH_2$ or $-NH_p$-Pg, where p is 0 or 1;

R^2 and R^3 are independently $-OR^{2a}$, or $-N(R^{2b})(R^{2c})$,

where

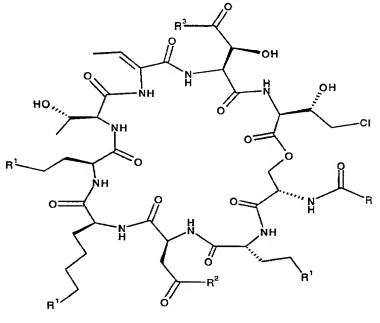
R^{2a} and R^{2b} are independently hydrogen, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, hydroxy(C_1-C_{10})alkyl, alkoxy(C_1-C_{10})alkyl, C_2-C_{10} alkenyl, amino(C_1-C_{10})alkyl, mono- or di-alkylamino(C_1-C_{10})alkyl, aryl(C_1-C_{10})alkyl, heteroaryl(C_1-C_{10})alkyl, or cycloheteroalkyl(C_1-C_{10})alkyl, or

R^{2b} is an alkyl carboxylate residue of an aminoacid alkyl ester, and

R^{2c} is hydrogen or C_1-C_6 alkyl,

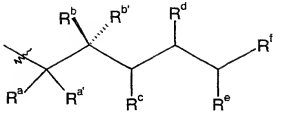
provided that both R^2 and R^3 are not -OH; and pharmaceutically acceptable salts and solvates thereof.

2. A pseudomycin prodrug having the following structure



wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

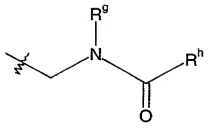
R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_8-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

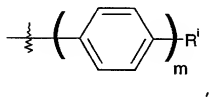


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

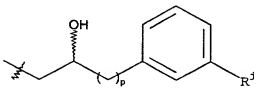
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

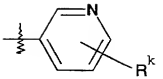


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

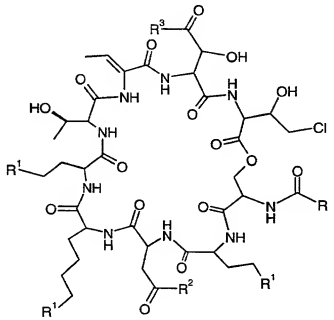
R is $-(CH_2)-NR^m-(C_{13}-C_{18}$ alkyl), where R^m is H, $-CH_3$ or $-C(O)CH_3$;

R^1 is independently $-NH_2$ or $-NH_p-Pg$, where p is 0 or 1;

R^2 and R^3 are $-OR^{2a}$, where R^{2a} is C_1-C_3 alkyl; and pharmaceutically acceptable salts and solvates thereof.

3. A 3-amido derivative of a pseudomycin compound prepared by the steps of

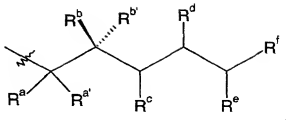
(i) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

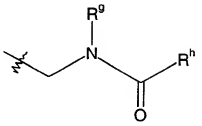
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic

ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

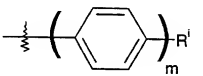


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

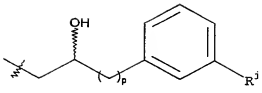
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

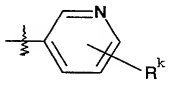


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is $-(CH_2)-NR^m-(C_{13}$-C_{18} alkyl), where R^m is H, $-CH_3$ or $-C(C)CH_3$;

R^1 is $-NH_2$;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

(ii) protecting the amino groups, R^1, at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 3 using *o*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate or 2(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate as a coupling agent;

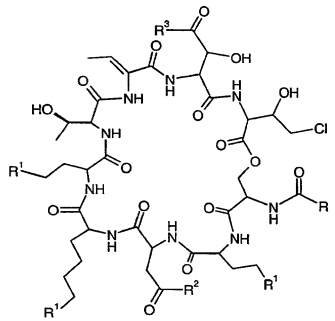
(iv) removing said amino-protecting groups.

4. The 3-amido derivative of Claim 3 wherein step (iii) forming an amide linkage is accomplished in the presence of a bulky amine.

5. The 3-amido derivative of Claim 3 wherein step (iii) forming an amide linkage is accomplished in the presence of a bulky amine and at a temperature between about 0°C and -20°C.

6. An 8-amido derivative of a pseudomycin compound prepared by the steps of

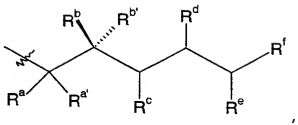
(i) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

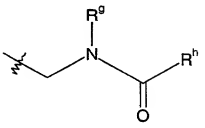
R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14}

alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

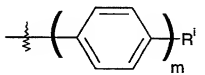


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

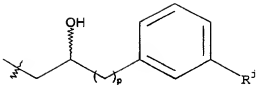
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

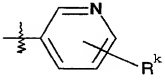


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is $-(CH_2)-NR^m-(C_{13}$-C_{18} alkyl), where R^m is H, $-CH_3$ or $-C(C)CH_3$;

R^1 is $-NH_2$;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

(ii) protecting the amino groups at positions 2, 4 and 5 with an amino-protecting group;

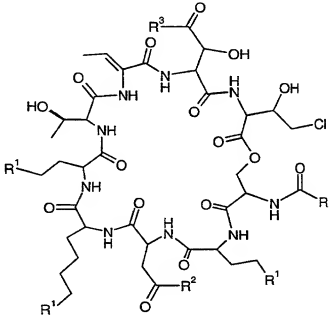
(iii) forming an amide linkage at position 8 using benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate as a coupling agent;

(iv) removing said amino-protecting groups.

7. The use of a compound as claimed in any one of the preceding claims in the preparation of a medicament for use in combating either systemic fungal infections or fungal skin infections.

8. A process for making a 3-amido derivative of a pseudomycin compound comprising the steps of

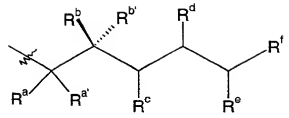
(i) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

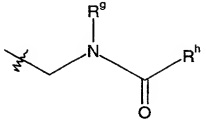
R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_5 cycloalkyl ring;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

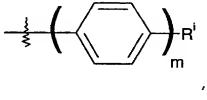


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

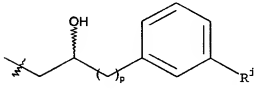
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

R is

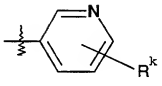


where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and

p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is $-(CH_2)-NR^m-(C_{13}$-C_{18} alkyl), where R^m is H, $-CH_3$ or $-C(C)CH_3$;

R^1 is $-NH_2$;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

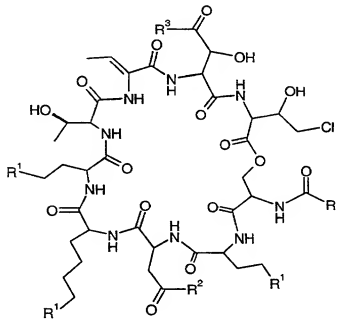
(ii) protecting the amino groups, R^1, at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 3 using *o*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate or 2(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate as a coupling agent in the presence of a bulky amine and at a temperature between about 0°C and -20°C;

(iv) removing said amino-protecting groups.

9. A process for making an 8-amido derivative of a pseudomycin compound comprising the steps of

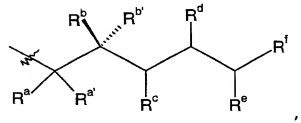
(ii) providing a pseudomycin compound having the following structure



I

wherein

R is



where

R^a and $R^{a'}$ are independently hydrogen or methyl, or either R^a or $R^{a'}$ is alkyl amino, taken together with R^b or $R^{b'}$ forms a six-

membered cycloalkyl ring, a six-membered aromatic ring or a double bond, or taken together with R^c forms a six-membered aromatic ring;

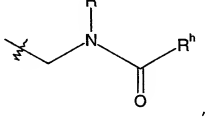
R^b and $R^{b'}$ are independently hydrogen, halogen, or methyl, or either R^b or $R^{b'}$ is amino, alkylamino, α-acetoacetate, methoxy, or hydroxy;

R^c is hydrogen, hydroxy, C_1-C_4 alkoxy, hydroxy(C_1-C_4)alkoxy, or taken together with R^e forms a 6-membered aromatic ring or C_5-C_6 cycloalkyl ring;

R^e is hydrogen, or taken together with R^f is a six-membered aromatic ring, C_5-C_{14} alkoxy substituted six-membered aromatic ring, or C_5-C_{14} alkyl substituted six-membered aromatic ring, and

R^f is C_6-C_{18} alkyl, C_5-C_{11} alkoxy or biphenyl;

R is

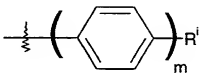


where

R^g is hydrogen, or C_1-C_{13} alkyl, and

R^h is C_1-C_{15} alkyl, C_4-C_{15} alkoxy, (C_1-C_{10} alkyl)phenyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-(C_5-C_6 cycloalkyl), where n = 1 or 2; or

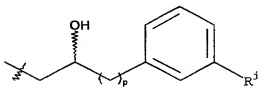
R is



where

R^i is a hydrogen, halogen, or C_5-C_8 alkoxy, and m is 1, 2 or 3;

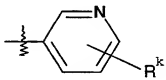
R is



where

R^j is C_5-C_{14} alkoxy or C_5-C_{14} alkyl, and p = 0, 1 or 2;

R is



where

R^k is C_5-C_{14} alkoxy; or

R is $-(CH_2)-NR^m-(C_{13}-C_{18}$ alkyl), where R^m is H, $-CH_3$ or $-C(C)CH_3$;

R^1 is $-NH_2$;

R^2 and R^3 are -OH; and

pharmaceutically acceptable salts and solvates thereof;

(ii) protecting the amino groups at positions 2, 4 and 5 with an amino-protecting group;

(iii) forming an amide linkage at position 8 using benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate as a coupling agent;

(iv) removing said amino-protecting groups.

10. A pharmaceutical formulation comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

11. A pharmaceutical formulation comprising a prodrug of Claim 2 and a pharmaceutically acceptable carrier.

12. A method for treating an antifungal infection in an aminal in need thereof, which comprises administering to said animal a pseudomycin compound of Claim 1.

13. A method for treating an antifungal infection in an animal in need thereof, which comprises administering to said animal a prodrug of Claim 2.

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

Attorney Docket Number	X-11811
First Named Inventor	Shu Hui Chen
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

[X] Declaration Submitted with Initial Filing

[ ] Declaration Submitted after Initial Filing

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PSEUDOMYCIN AMIDE AND ESTER ANALOGS

the specification of which
[ ] is attached hereto
OR
[X] was filed on (MM/DD/YYYY) 08 June 2000 as United States Application Number or PCT International

Application Number PCT/US00/15021 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached YES	NO
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]

[ ] Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional applications(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)
60/143,981	15 July 1999

[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Attorney Name	Reg. No.
Arvie J. Anderson	45,263
Lynn D. Apelgren	45,341
Robert A. Armitage	27,417
Brian P. Barrett	39,597
Michael T. Bates	34,121
Roger S. Benjamin	27,025
Gary M. Birch	48,881
William R. Boudreaux	35,796
Steven P. Caltrider	35,467
Paul R. Cantrell	36,470
Charles E. Cohen	34,565
Donald L. Comeglio	30,741
Gregory A. Cox	47,504
Paula K. Davis	47,517
Elizabeth A. Dawalt	44,646
John C. Demeter	30,167
Manisha A. Desai	43,565
Joanne Longo Feeney	35,134
Paul J. Gaylo	36,808
Francis O. Ginah	44,712
Janet A. Gongola	48,436
Amy E. Hamilton	33,894
Frederick D. Hunter	26,915
Thomas E. Jackson	33,064
Charles Joyner	30,466
Gerald P. Kelleher	43,707

Attorney Name	Reg. No.
James J. Kelley	41,888
Paul J. Koivuniemi	31,533
Robert E. Lee	27,919
Kirby Lee	47,744
James P. Leeds	35,241
Nelsen L. Lentz	38,537
Douglas K. Norman	33,267
Arleen Palmberg	40,422
Thomas G. Plant	35,784
Edward Prein	37,212
Grant E. Reed	41,264
James J. Sales	33,773
Michael J. Sayles	32,295
Robert L. Sharp	45,609
David M. Stemerick	40,187
Mark J. Stewart	43,936
Robert D. Titus	40,206
Robert C. Tucker	45,165
Tina M. Tucker	47,145
MaCharri Vomdran-Jones	36,711
Gilbert T. Voy	43,972
Thomas D. Webster	39,872
Lawrence T. Welch	29,487
Alexander Wilson	45,782
Dan L. Wood	48,613

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to.

Name	**ELI LILLY AND COMPANY**						
Address	**ATTN: TINA M. TUCKER**						
Address	**LILLY CORPORATE CENTER/DC1104**						
City	**INDIANAPOLIS**	**State**	**INDIANA**		**ZIP**	**46285**	
Country		**Telephone**	**(317) 277-3537**		**Fax**	**(317) 276-3861**	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ **A Petition has been filed for this unsigned inventor**

Given Name	**Shu**	**Middle Name**	**Hui**	**Family Name**	**Chen**	**Suffix e.g. Jr.**	
Inventor's Signature						**Date**	
Residence: City	**Carmel**	**State**	**IN**	**Country**	**USA**	**Citizenship**	**USA**
Address	**13256 Snow Owl Drive**						
Post Office Address	SAME AS ABOVE						
City	**Carmel**	**State**	**IN**	**Zip**	**46033**	**Country**	**USA**

[x] **Additional Inventors are being named on supplement sheet(s) attached hereto.**

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PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

Name of Additional Joint Inventor, if any:										☐ A Petition has been filed for this unsigned inventor
Given Name	Christopher	Middle Name	Stanley	Family Name	Galka	Suffix e.g. Jr.				
Inventor's Signature						Date				
Residence: City	Carmel	State	IN	Country	USA	Citizenship	USA			
Address	13690 N. Stone Haven Drive									
Post Office Address	SAME AS ABOVE									
City	Carmel	State	IN	Zip	46033	Country	USA			

Name of Additional Joint Inventor, if any:										☐ A Petition has been filed for this unsigned inventor
Given Name	Sarah	Middle Name	Lynne	Family Name	Hellman	Suffix e.g. Jr.				
Inventor's Signature						Date				
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA			
Post Office Address	7009 Ringtail Court									
Post Office Address	SAME AS ABOVE									
City	Indianapolis	State	IN	Zip	46254	Country	USA			

Name of Additional Joint Inventor, if any:										☐ A Petition has been filed for this unsigned inventor
Given Name	John	Middle Name	L.	Family Name	Krstenansky	Suffix e.g. Jr.				
Inventor's Signature						Date				
Residence: City	Belmont	State	MA	Country	USA	Citizenship	USA			
Post Office Address	63 Kilburn Road									
Post Office Address	SAME AS ABOVE									
City	Belmont	State	MA	Zip	02478	Country	USA			

Name of Additional Joint Inventor, if any:										☐ A Petition has been filed for this unsigned inventor
Given Name	Michael	Middle Name	John	Family Name	Rodriguez	Suffix e.g. Jr.				
Inventor's Signature						Date				
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA			
Post Office Address	7649 Gordonshire Court									
Post Office Address	SAME AS ABOVE									
City	Indianapolis	State	IN	Zip	46278	Country	USA			

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PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

Name of Additional Joint Inventor, if any:									
☐ A Petition has been filed for this unsigned inventor									
Given Name	Xicheng	Middle Name	David	Family Name	Sun	Suffix e.g. Jr.			
Inventor's Signature						Date	11/30/2001		
Residence: City	Superior	State	CO	Country	USA	Citizenship	China		
Address	923 Grays Peak Drive								
Post Office Address	SAME AS ABOVE								
City	Superior	State	CO	Zip	80027	Country	USA		

Name of Additional Joint Inventor, if any:									
☐ A Petition has been filed for this unsigned inventor									
Given Name	Alexander	Middle Name	Ya	Family Name	Usyatinsky	Suffix e.g. Jr.			
Inventor's Signature						Date			
Residence: City	Troy	State	NY	Country	USA	Citizenship	USA		
Post Office Address	6 Aavelord Boulevard								
Post Office Address	SAME AS ABOVE								
City	Troy	State	NY	Zip	12180	Country	USA		

Name of Additional Joint Inventor, if any:									
☐ A Petition has been filed for this unsigned inventor									
Given Name	Venkatraghavan	Middle Name		Family Name	Vasudevan	Suffix e.g. Jr.			
Inventor's Signature						Date			
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA		
Post Office Address	1016 Saratoga Circle								
Post Office Address	SAME AS ABOVE								
City	Indianapolis	State	IN	Zip	46280	Country	USA		

Name of Additional Joint Inventor, if any:									
☐ A Petition has been filed for this unsigned inventor									
Given Name	Mark	Middle Name	James	Family Name	Sweifel	Suffix e.g. Jr.			
Inventor's Signature						Date			
Residence: City	Mooresville	State	IN	Country	USA	Citizenship	USA		
Post Office Address	1840 Centenary Road								
Post Office Address	SAME AS ABOVE								
City	Mooresville	State	IN	Zip	46158	Country	USA		

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

Attorney Docket Number	**X-11811**
First Named Inventor	**Shu Hui Chen**
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

[X] Declaration Submitted with Initial Filing
[ ] Declaration Submitted after Initial Filing

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PSEUDOMYCIN AMIDE AND ESTER ANALOGS

the specification of which
[ ] is attached hereto
OR
[X] was filed on (MM/DD/YYYY) 08 June 2000 as United States Application Number or PCT International
Application Number PCT/US00/15021 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached YES	NO
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]

[ ] Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional applications(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)
60/143,981	15 July 1999

[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

Please type a plus sign (+) inside this box ☐ [+]

PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

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As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Attorney Name	Reg. No.
Arvie J. Anderson	45,263
Lynn D. Apelgren	45,341
Robert A. Armitage	27,417
Brian P. Barrett	39,597
Michael T. Bates	34,121
Roger S. Benjamin	27,025
Gary M. Birch	48,881
William R. Boudreaux	35,796
Steven P. Caltrider	36,467
Paul R. Cantrell	36,470
Charles E. Cohen	34,565
Donald L. Corneglio	30,741
Gregory A. Cox	47,504
Paula K. Davis	47,517
Elizabeth A. Dawalt	44,646
John C. Demeter	30,167
Manisha A. Desai	43,585
Joanne Longo Feeney	35,134
Paul J. Gaylo	36,808
Francis O. Ginah	44,712
Janet A. Gongola	48,436
Amy E. Hamilton	33,894
Frederick D. Hunter	26,915
Thomas E. Jackson	33,064
Charles Joyner	30,466
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Paul J. Koivuniemi	31,533
Robert E. Lee	27,919
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James P. Leeds	35,241
Nelsen L. Lentz	38,537
Douglas K. Norman	33,267
Arleen Palmberg	40,422
Thomas G. Plant	35,784
Edward Prein	37,212
Grant E. Reed	41,264
James J. Sales	33,773
Michael J. Sayles	32,295
Robert L. Sharp	45,609
David M. Stemerick	40,187
Mark J. Stewart	43,936
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Robert C. Tucker	45,165
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MaCharri Vorndran-Jones	36,711
Gilbert T. Voy	43,972
Thomas D. Webster	39,872
Lawrence T. Welch	29,487
Alexander Wilson	45,782
Dan L. Wood	48,613

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

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Address	ATTN: TINA M. TUCKER						
Address	LILLY CORPORATE CENTER/DC1104						
City	INDIANAPOLIS	**State**	INDIANA	**ZIP**	46285		
Country		**Telephone**	(317) 277-3537	**Fax**	(317) 276-3861		

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Name of Sole or First Inventor: ☐ **A Petition has been filed for this unsigned inventor**

Given Name	Shu	**Middle Name**	Hui	**Family Name**	Chen	**Suffix** e.g. Jr.	
Inventor's Signature						**Date**	
Residence: City	Carmel	**State**	IN	**Country**	USA	**Citizenship**	USA
Address	13256 Snow Owl Drive						
Post Office Address	SAME AS ABOVE						
City	Carmel	**State**	IN	**Zip**	46033	**Country**	USA

[x] **Additional Inventors are being named on supplement sheet(s) attached hereto.**

Please type a plus sign (+) inside this box ☐ [+]

PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

Name of Additional Joint Inventor, if any:				☐ A Petition has been filed for this unsigned inventor			
Given Name	Christopher	Middle Name	Stanley	Family Name	Galka	Suffix e.g. Jr.	
Inventor's Signature					Date		
Residence: City	Carmel	State	IN	Country	USA	Citizenship	USA
Address	13690 N. Stone Haven Drive						
Post Office Address	SAME AS ABOVE						
City	Carmel	State	IN	Zip	46033	Country	USA

Name of Additional Joint Inventor, if any:				☐ A Petition has been filed for this unsigned inventor			
Given Name	Sarah	Middle Name	Lynne	Family Name	Hellman	Suffix e.g. Jr.	
Inventor's Signature					Date		
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA
Post Office Address	7009 Ringtail Court						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46254	Country	USA

Name of Additional Joint Inventor, if any:				☐ A Petition has been filed for this unsigned inventor			
Given Name	John	Middle Name	L.	Family Name	Krstenansky	Suffix e.g. Jr.	
Inventor's Signature					Date		
Residence: City	Belmont	State	MA	Country	USA	Citizenship	USA
Post Office Address	63 Kilburn Road						
Post Office Address	SAME AS ABOVE						
City	Belmont	State	MA	Zip	02478	Country	USA

Name of Additional Joint Inventor, if any:				☐ A Petition has been filed for this unsigned inventor			
Given Name	Michael	Middle Name	John	Family Name	Rodriguez	Suffix e.g. Jr.	
Inventor's Signature					Date		
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA
Post Office Address	7649 Gordonshire Court						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46278	Country	USA

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PTO/SB/01 (8-96) (MODIFIED)

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	Xicheng	Middle Name	David	Family Name	Sun	Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City	Superior	State	CO	Country	USA	Citizenship	China
Address	923 Grays Peak Drive						
Post Office Address	SAME AS ABOVE						
City	Superior	State	CO	Zip	80027	Country	USA

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	Alexander	Middle Name	Ya	Family Name	Usyatinsky	Suffix e.g. Jr.	
Inventor's Signature	[signature]					Date	11.30.01
Residence: City	Troy	State	NY	Country	USA	Citizenship	USA
Post Office Address	6 Aavelord Boulevard						
Post Office Address	SAME AS ABOVE						
City	Troy	State	NY	Zip	12180	Country	USA

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	Venkatraghavan	Middle Name		Family Name	Vasudevan	Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA
Post Office Address	1016 Saratoga Circle						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46280	Country	USA

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	Mark	Middle Name	James	Family Name	Sweifel	Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City	Mooresville	State	IN	Country	USA	Citizenship	USA
Post Office Address	1840 Centenary Road						
Post Office Address	SAME AS ABOVE						
City	Mooresville	State	IN	Zip	46158	Country	USA

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

[X] Declaration Submitted with Initial Filing

[ ] Declaration Submitted after Initial Filing

Attorney Docket Number	**X-11811**
First Named Inventor	**Shu Hui Chen**
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named Inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole Inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PSEUDOMYCIN AMIDE AND ESTER ANALOGS

the specification of which
[ ] is attached hereto
OR
[X] was filed on (MM/DD/YYYY) 08 June 2000 as United States Application Number or PCT International
Application Number PCT/US00/15021 and was amended on (MM/DD/YYYY) [ ] (if applicable).

II hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or Inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached YES	NO
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
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I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional applications(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)
60/143,981	15 July 1999

[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

Please type a plus sign (+) inside this box [+]
☐

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Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

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U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

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Gregory A. Cox	47,504
Paula K. Davis	47,517
Elizabeth A. Dawalt	44,646
John C. Demeter	30,167
Manisha A. Desai	43,585
Joanne Longo Feeney	35,134
Paul J. Gaylo	36,808
Francis O. Ginah	44,712
Janet A. Gongola	48,436
Amy E. Hamilton	33,894
Frederick D. Hunter	26,915
Thomas E. Jackson	33,064
Charles Joyner	30,466
Gerald P. Kelleher	43,707

Attorney Name	Reg. No.
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Paul J. Kolvuniemi	31,533
Robert E. Lee	27,619
Kirby Lee	47,744
James P. Leeds	35,241
Nelsen L. Lentz	38,537
Douglas K. Norman	33,267
Arleen Palmberg	40,422
Thomas G. Plant	35,784
Edward Prein	37,212
Grant E. Reed	41,264
James J. Sales	33,773
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Direct all correspondence to:

Name	**ELI LILLY AND COMPANY**						
Address	**ATTN: TINA M. TUCKER**						
Address	**LILLY CORPORATE CENTER/DC1104**						
City	**INDIANAPOLIS**	**State**	**INDIANA**	**ZIP**	**46285**		
Country		**Telephone**	**(317) 277-3537**	**Fax**	**(317) 276-3861**		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ **A Petition has been filed for this unsigned inventor**

Given Name	Middle Name	Family Name	Suffix e.g. Jr.
Shu	**Hui**	**Chen**	

Inventor's Signature **Date**

Residence: City	**Carmel**	**State**	**IN**	**Country**	**USA**	**Citizenship**	**USA**
Address	**13256 Snow Owl Drive**						
Post Office Address	SAME AS ABOVE						
City	**Carmel**	**State**	**IN**	**Zip**	**46033**	**Country**	**USA**

[X] **Additional Inventors are being named on supplement sheet(s) attached hereto.**

Please type a plus sign (+) inside this box [+]

DECLARATION

Name of Additional Joint Inventor, if any:				[ ] A Petition has been filed for this unsigned inventor					
Given Name	Christopher	Middle Name	Stanley	Family Name	Galka			Suffix e.g. Jr.	
Inventor's Signature						Date			
Residence: City	Carmel	State	IN	Country	USA			Citizenship	USA
Address	13690 N. Stone Haven Drive								
Post Office Address	SAME AS ABOVE								
City	Carmel	State	IN	Zip	46033	Country	USA		

Name of Additional Joint Inventor, if any:				[ ] A Petition has been filed for this unsigned inventor					
Given Name	Sarah	Middle Name	Lynne	Family Name	Hellman			Suffix e.g. Jr.	
Inventor's Signature						Date			
Residence: City	Indianapolis	State	IN	Country	USA			Citizenship	USA
Post Office Address	7009 Ringtail Court								
Post Office Address	SAME AS ABOVE								
City	Indianapolis	State	IN	Zip	46254	Country	USA		

Name of Additional Joint Inventor, if any:				[ ] A Petition has been filed for this unsigned inventor					
Given Name	John	Middle Name	L.	Family Name	Krstenansky			Suffix e.g. Jr.	
Inventor's Signature						Date	12/1/01		
Residence: City	Belmont	State	MA	Country	USA			Citizenship	USA
Post Office Address	63 Kilburn Road								
Post Office Address	SAME AS ABOVE								
City	Belmont	State	MA	Zip	02478	Country	USA		

Name of Additional Joint Inventor, if any:				[ ] A Petition has been filed for this unsigned inventor					
Given Name	Michael	Middle Name	John	Family Name	Rodriguez			Suffix e.g. Jr.	
Inventor's Signature						Date			
Residence: City	Indianapolis	State	IN	Country	USA			Citizenship	USA
Post Office Address	7649 Gordonshire Court								
Post Office Address	SAME AS ABOVE								
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PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	Xicheng	Middle Name	David	Family Name	Sun	Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City	Superior	State	CO	Country	USA	Citizenship	China
Address	923 Grays Peak Drive						
Post Office Address	SAME AS ABOVE						
City	Superior	State	CO	Zip	80027	Country	USA

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	Alexander	Middle Name	Ya	Family Name	Usyatinsky	Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City	Troy	State	NY	Country	USA	Citizenship	USA
Post Office Address	6 Aavelord Boulevard						
Post Office Address	SAME AS ABOVE						
City	Troy	State	NY	Zip	12180	Country	USA

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	Venkatraghavan	Middle Name		Family Name	Vasudevan	Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA
Post Office Address	1016 Saratoga Circle						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46280	Country	USA

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Given Name	Mark	Middle Name	James	Family Name	Sweifel	Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City	Mooresville	State	IN	Country	USA	Citizenship	USA
Post Office Address	1840 Centenary Road						
Post Office Address	SAME AS ABOVE						
City	Mooresville	State	IN	Zip	46158	Country	USA

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

Attorney Docket Number	X-11811
First Named Inventor	Shu Hui Chen
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

[X] Declaration Submitted with Initial Filing
[ ] Declaration Submitted after Initial Filing

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My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole Inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PSEUDOMYCIN AMIDE AND ESTER ANALOGS

the specification of which
[ ] is attached hereto
OR
[X] was filed on (MM/DD/YYYY) 08 June 2000 as United States Application Number or PCT International Application Number PCT/US00/15021 and was amended on (MM/DD/YYYY) _____ (if applicable).

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Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached YES	Certified Copy Attached NO
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
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Application Number(s)	Filing Date (MM/DD/YYYY)
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U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

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Frederick D. Hunter	26,915
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Attorney Name	Reg. No.
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Robert E. Lee	27,919
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Douglas K. Norman	33,267
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Robert C. Tucker	45,165
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Lawrence T. Welch	29,487
Alexander Wilson	45,782
Dan L. Wood	48,613

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

Name	ELI LILLY AND COMPANY				
Address	ATTN: TINA M. TUCKER				
Address	LILLY CORPORATE CENTER/DC1104				
City	INDIANAPOLIS	**State**	INDIANA	**ZIP**	46285
Country		**Telephone**	(317) 277-3537	**Fax**	(317) 276-3861

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A Petition has been filed for this unsigned inventor

Given Name	Shu	**Middle Name**	Hui	**Family Name**	Chen	**Suffix e.g. Jr.**	
Inventor's Signature						**Date**	11/30/00
Residence: City	Carmel	**State**	IN	**Country**	USA	**Citizenship**	USA
Address	13256 Snow Owl Drive						
Post Office Address	SAME AS ABOVE						
City	Carmel	**State**	IN	**Zip**	46033	**Country**	USA

[x] **Additional Inventors are being named on supplement sheet(s) attached hereto.**

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	Christopher	Middle Name	Stanley	Family Name	Galka	Suffix e.g. Jr.	
Inventor's Signature					Date	12/7/01	
Residence: City	Carmel	State	IN	Country	USA	Citizenship	USA
Address	13690 N. Stone Haven Drive						
Post Office Address	SAME AS ABOVE						
City	Carmel	State	IN	Zip	46033	Country	USA

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	Sarah	Middle Name	Lynne	Family Name	Hellman	Suffix e.g. Jr.	
Inventor's Signature					Date	11/29/01	
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA
Post Office Address	7009 Ringtail Court						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46254	Country	USA

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	John	Middle Name	L.	Family Name	Krstenansky	Suffix e.g. Jr.	
Inventor's Signature					Date		
Residence: City	Belmont	State	MA	Country	USA	Citizenship	USA
Post Office Address	63 Kilburn Road						
Post Office Address	SAME AS ABOVE						
City	Belmont	State	MA	Zip	02478	Country	USA

Name of Additional Joint Inventor, if any:		☐ A Petition has been filed for this unsigned inventor					
Given Name	Michael	Middle Name	John	Family Name	Rodriguez	Suffix e.g. Jr.	
Inventor's Signature					Date	11/29/01	
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA
Post Office Address	7649 Gordonshire Court						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46278	Country	USA

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)

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DECLARATION

Name of Additional Joint Inventor, if any:		[ ] A Petition has been filed for this unsigned inventor					
Given Name	Xicheng	Middle Name	David	Family Name	Sun	Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City	Superior CO	State	CO	Country	USA	Citizenship	China
Address	923 Grays Peak Drive						
Post Office Address	SAME AS ABOVE						
City	Superior	State	CO	Zip	80027	Country	USA

Name of Additional Joint Inventor, if any:		[ ] A Petition has been filed for this unsigned inventor					
Given Name	Alexander	Middle Name	Ya	Family Name	Usyatinsky	Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City	Troy NY	State	NY	Country	USA	Citizenship	USA
Post Office Address	6 Aavelord Boulevard						
Post Office Address	SAME AS ABOVE						
City	Troy	State	NY	Zip	12180	Country	USA

Name of Additional Joint Inventor, if any:		[ ] A Petition has been filed for this unsigned inventor					
Given Name	Venkatraghavan	Middle Name		Family Name	Vasudevan	Suffix e.g. Jr.	
Inventor's Signature	Venkatraghavan Vasudevan					Date	12-12-01
Residence: City	Indianapolis IN	State	IN	Country	USA	Citizenship	USA
Post Office Address	1016 Saratoga Circle						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46280	Country	USA

Name of Additional Joint Inventor, if any:		[ ] A Petition has been filed for this unsigned inventor					
Given Name	Mark	Middle Name	James	Family Name	Zweifel	Suffix e.g. Jr.	
Inventor's Signature	Mark James Zweifel					Date	11-28-01
Residence: City	Mooresville IN	State	IN	Country	USA	Citizenship	USA
Post Office Address	1840 Centenary Road						
Post Office Address	SAME AS ABOVE						
City	Mooresville	State	IN	Zip	46158	Country	USA